CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of pentachlorophenol. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to pentachlorophenol, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to pentachlorophenol was also conducted; the results of this review are presented in Appendix C.

Animal oral studies are presented in Table 2-2 and Figure 2-2; no inhalation or dermal data were identified for pentachlorophenol.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects (SLOAELs) are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant

dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of pentachlorophenol are indicated in Table 2-2 and Figure 2-2.

A User's Guide has been provided at the end of this profile (see Appendix D). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

The production of pentachlorophenol introduces a number of contaminants; typical contaminants found in technical-grade and commercial-grade pentachlorophenol include other chlorophenols, CDDs, CDFs, hexachlorobenzene, and chlorophenoxy compounds. Pure pentachlorophenol is typically ≥98% pure with very low levels of CDDs and CDFs.

Technical-grade pentachlorophenol typically contains 85–90% pentachlorophenol. Two commonly used commercial-grade pentachlorophenols, Dowicide EC-7 (EC-7) and Dow PCP DP-2 (DP-2), are typically 90% pentachlorophenol and contain lower levels of CDDs and CDFs than technical-grade pentachlorophenol. A number of animal studies evaluated potential differences in the toxicity of pure pentachlorophenol, technical-grade pentachlorophenol, and/or commercial-grade pentachlorophenol. These studies demonstrate that some of the effects observed for technical-grade pentachlorophenol are due to the contaminants rather than the pentachlorophenol and that the contaminant may influence pentachlorophenol potency. NTP (1989) analyzed the samples of pure pentachlorophenol, technical-grade pentachlorophenol, EC-7, and DP-2; the results of these analyzes are presented in Table 2-1.

Table 2-1. Analysis of Impurities Present in Pentachlorophenol Used in NTP (1989) Studies

Contaminant	Pure	Technical grade	EC-7[a]	DP-2
Dichlorophenol	–	–	–	0.0013%[b]
Trichlorophenol	<0.01%	0.01%	0.007%[c]	0.044%[d]
Tetrachlorophenol	1.4%	3.8%	9.4%	7.0%[e]
Hexachlorobenzene	10 ppm	50 ppm	65 ppm	15 ppm
Tetrachlorodibenzodioxin	<0.08 ppm	–	<0.04 ppm	–
Hexachlorodibenzodioxin	<1 ppm	10.1 ppm	0.19 ppm	0.59 ppm
Heptachlorodibenzodioxin	–	296 ppm	296 ppm	28 ppm
Octachlorodibenzodioxin	<1 ppm	1,386 ppm	1,386 ppm	173 ppm
Pentachlorodibenzofuran	–	1.4 ppm	1.4 ppm	–
Hexachlorodibenzofuran	–	9.9 ppm	9.9 ppm	12.95 ppm
Heptachlorodibenzofuran	–	88 ppm	88 ppm	172 ppm
Octachlorodibenzofuran	–	43 ppm	43 ppm	320 ppm
Heptachlorohydroxydiphenyl ether	0.01%	0.11%[f]	0.11%	0.05%[f]
Octachlorohydroxydiphenyl ether	0.09%	1.91%	1.91%	1.41%
Nonachlorohydroxydiphenyl ether	0.21%	3.56%	3.56%	2.21%
Hexachlorohydroxydibenzofuran	0.11%	0.16%	0.16%	0.07%
Heptachlorohydroxydibenzofuran	0.22%	0.47%	0.47%	0.31%
Hexachlorohydroxybiphenyl and heptachlorohydroxybiphenyl	--	--	--	Detected[g]

[a]Four unidentified impurities with concentrations of 0.14, 0.057, 0.045, and 0.035 ppm were also detected.
[b]Probably the 2,4-isomer.
[c]Identified as the 2,3,6-siomer; another isomer was believed to be present but not identified.
[d]Probably the 2,4,5-isomer.
[e]Probably the 2,3,4,6-isomer.
[f]Includes octachlorodiphenyl ether.
[g]Two isomers each of hexachlorohydroxybiphenyl and heptachlorohydroxybiphenyl.

Source: NTP 1989

The health effects of pentachlorophenol have been evaluated in epidemiological and laboratory animal studies. As illustrated in Figure 2-1, most of the health effects data come from oral exposure studies in animals and inhalation studies in humans. Animal data are available for most health effect categories (no dermal effects data are available) and all exposure duration categories. The most examined endpoints were body weight (approximately 60% of the animal studies examined this endpoint), hepatic (approximately 40%), and immunological (approximately 30%). One inhalation exposure study and one dermal exposure study in experimental animals were identified. A number of observational epidemiological studies examined most endpoints. Interpretation of many of the human studies is limited by the small number of subjects (many are case reports of individuals), poor exposure information, and

exposure to other chemicals. Some studies have suggested associations between pentachlorophenol exposure and an adverse health outcome; most of the studies are cross-sectional in design and do not establish causality.

The human and animal studies suggest several sensitive targets of pentachlorophenol toxicity (see Appendix C for details on the systematic review):

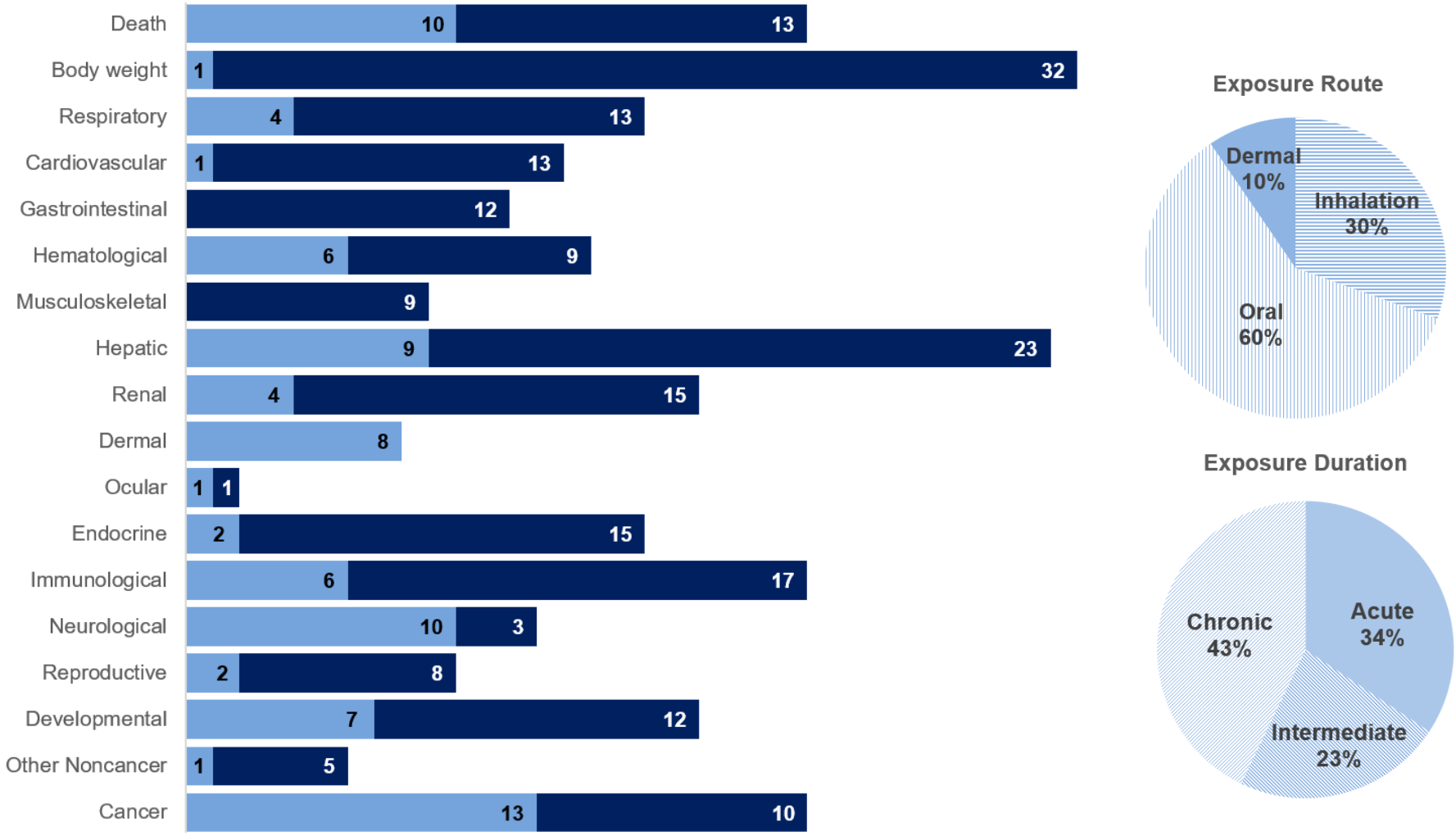
- **Hepatic Endpoints:** Hepatic effects are a presumed health effect for humans based on limited evidence in humans and strong evidence in rats, mice, and dogs exposed to pure pentachlorophenol, commercial-grade pentachlorophenol, and/or technical-grade pentachlorophenol. The observed effects include increases in liver weight, hepatocellular hypertrophy, hepatocellular degeneration and necrosis, and chronic inflammation.

- **Developmental Endpoints:** Developmental effects are a presumed health effect for humans based on limited evidence in humans and strong evidence in animals in rats. Developmental effects include increased resorptions, decreases in litter size, and decreases in fetal/pup body weight in animals exposed to pure pentachlorophenol or technical-grade pentachlorophenol.

Other adverse effects have been reported including gastrointestinal irritation, hematological alterations, and impaired immune responses. However, these effects have not been consistently observed across studies or were attributed to exposure to pentachlorophenol contaminants.

Figure 2-1. Overview of the Number of Studies Examining Pentachlorophenol Health Effects*

Most studies examined the potential body weight, hepatic, and immunological effects of pentachlorophenol
Fewer studies evaluated health effects in humans than animals (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 100 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Bekhouche et al. 2019									**Purity not reported**
1	Rat (Wistar) 6F	2 weeks (GW)	0, 20	BC, BI, HP	Hepatic		20		Increased serum AST and ALT; hepatocellular necrosis, binucleated and pyknotic hepatocytes, dilation and congestion of the centrilobular vein and sinusoids
Bernard and Hoberman 2001									**Tech (89%)**
2	Rat (Sprague-Dawley) 25F	GDs 6–15 (GO)	0, 10, 30, 80	CS, BW, FI, DX	Bd wt	30	80		Decreased maternal body weight (21% lower than controls on GDs 6–16)
					Develop	30		80	Increased resorptions, decreased fetal body weights and increased incidences of soft tissue (slight to moderate dilation of the kidneys) and skeletal ossification, malformations and variations
Deichmann et al. 1942									**Tech (purity not reported)**
3	Rat (Wistar) 60NS	Once (GO)	NS	LE, CS	Death			78	LD_{50}
Deichmann et al. 1942									**Tech NaPCP**
4	Rat (Wistar) 60NS	Once (G)	NS	LE, CS	Death			210.6	LD_{50}
Schwetz et al. 1974									**Pure (>98%)**
5	Rat (Sprague-Dawley) 15–33F	GDs 6–15 (GO)	0, 5, 15, 30, 50	BW, DX	Bd wt	15		30	74% decrease in maternal weight gain
					Develop		5[b]	30	Delayed ossification of skull at 5 mg/kg/day; increased incidence of subcutaneous edema and skeletal anomalies at ≥15 mg/kg/day; increased incidence of fetal resorptions (97% of fetuses resorbed) and marked decrease in fetal body weights at ≥30 mg/kg/day

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Schwetz et al. 1974									**Pure (>98%)**
6	Rat (Sprague-Dawley) 16F	GDs 8–11 (GO)	0, 30	BW, DX	Bd wt			30	67% decrease in maternal body weight gain on GDs 6-21
					Develop			30	Increased incidence fetal resorptions (64% of litters affected); skeletal and soft tissue anomalies; 42% decreased fetal body weight
Schwetz et al. 1974									**Pure (>98%)**
7	Rat (Sprague-Dawley) 20F	GDs 12–15 (GO)	0, 30	BW, DX	Bd wt	30			
					Develop		30		Soft tissue and skeletal anomalies; decreased fetal body weight and crown-rump length
Schwetz et al. 1974									**Tech (88.4% pure)**
8	Rat (Sprague-Dawley) 15–19F	GDs 6–15 (GO)	0, 5, 15, 30, 50	BW, DX	Bd wt	15		30	Decreased maternal body weight gain (25 and 45% in the 30 and 50 mg/kg/day groups, respectively)
					Develop	5		15	Fetal resorptions (64% of litters affected), subcutaneous edema, lumbar spurs
Schwetz et al. 1974									**Tech (88.4% pure)**
9	Rat (Sprague-Dawley) 19F	GDs 8–11 (GO)	0, 30	BW, DX	Bd wt		30		27% decrease in maternal weight gain on GDs 6-21
					Develop			30	Increased incidence of fetal resorptions; skeletal and soft tissue anomalies; 25% decreased fetal body weight
Schwetz et al. 1974									**Tech (88.4% pure)**
10	Rat (Sprague-Dawley) 17F	GDs 12–15 (GO)	0, 30	BW, DX	Bd wt	30			
					Develop		30		Increased incidence of sternebrae variations

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
St. Omer and Gadusek 1987									**Tech (purity not reported)**
11	Rat (Sprague-Dawley) 45–75B	Once (G)	31-449	LE, CS	Death			50	Age-specific LD_{50} values: 50 mg/kg at age 10 days, 108 mg/kg at 20 days, 220–230 mg/kg at 25–50 days, 120 mg/kg at 70 days, 80 mg/kg at 127–134 days
Borzelleca et al. 1985									**Pure (approx. 99%)**
12	Mouse (ICR) NS B	Once (G)	NS	LE, CS	Death			117 F 177 M	LD_{50}
Chen et al. 2013a									**Pure (>99%)**
13	Mouse (BALB/c) 4–5F	7 or 14 days 3 times/week (GO)	0, 6	BW, OW, IX	Bd wt	6			
					Immuno		6		Increased IL-2, IL-5, and IL-10 levels and decreased OVA-specific antibodies (IgG and IgM)
Holsapple et al. 1987									**EC-7 (90.4% pure)**
14	Mouse (B6C3F1) 8F	14 days (GO)	100	IX	Immuno	100			
Holsapple et al. 1987									**Tech (purity not reported)**
15	Mouse (B6C3F1) 8F	14 days (GO)	10, 30, 100	IX	Immuno		10[c]		Decreased response to sRBC
Kerkvliet et al. 1985a									**Tech (86% pure)**
16	Mouse (C57BL/6) 6 NS	1–2 days (GO)	15, 30, 60	OW, CS, IX	Immuno		83[c]		50% decrease in splenic response to sRBC
Kerkvliet et al. 1985a									**Pure (>99%)**
17	Mouse (C57BL/6) 6 NS	1–2 days (GO)	0, 15, 30, 60	OW, IX	Immuno	60			

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Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Renner et al. 1986									**Pure (99%)**
18	Mouse (NMRJ) 10M, 10F	Once (GO)	NS	LE, CS	Death			134 F 129 M	LD_{50}
Umemura et al. 1996									**Pure (98.6%)**
19	Mouse (B6C3F1) 30M	2 weeks (F)	0, 41, 86, 200	BC, BI, HP	Hepatic		41		Increased liver weight and severe hepatocyte swelling
White and Anderson 1985									**Tech (90.4% pure)**
20	Mouse (B6C3F1) NS F	14 days (GO)	0, 10, 30, 100	IX	Immuno	30	100[c]		Inhibition of compliment activity
White and Anderson 1985									**EC-7 (90.4% pure)**
21	Mouse (B6C3F1) NS F	14 days (GO)	0, 100	IX	Immuno	100			
Bernard et al. 2001									**Tech (88-89% pure)**
22	Rabbit (New Zealand) 20F	GD 6–18 (GO)	0, 7.5, 15, 30	BW, DX	Bd wt	7.5	15	30	Transient decrease in maternal body weight gain on GDs 9–12 at 15 mg/kg/day and maternal weight loss at 30 mg/kg/day
					Develop	30			
INTERMEDIATE EXPOSURE									
Bernard et al. 2002									**Tech (89% pure)**
23	Rat (Sprague-Dawley) 30M, 30F	P0: 70 days premating, and through gestation and lactation (GO)	0, 10, 30, 60	CS, BW, FI, HP, RX, DX	Bd wt		60		Decreased body weight gain 10-12% in P0 and 28–29% in F1
					Hepatic		10		Increased absolute and relative liver weight and hepatocellular hypertrophy ≥10 mg/kg/day; hepatocellular necrosis at ≥30 mg/kg/day

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Repro	60 F			
						10 M	30 M		Decreased average testicular spermatid counts in F1 males; decreased fertility at 60 mg/kg/day
					Develop		10	60	Decreased pup body weight on LDs 1 and 4 in F1 pups at 10 mg/kg/day and LDs 1, 4, and 28 at 30 and 60 mg/kg/day; decreased pup litter size and survival at 60 mg/kg/day
Blakley et al. 1998									**Pure (>99%)**
24	Rat (Fischer-344) 10M	28 days 2 times/week (GO)	0, 2.0	BW, IX, OW	Immuno		2		Enhanced lymphocyte blastogenesis, suppressed antibody response against sRBC
Exon and Koller 1982									**Tech (85% pure)**
25	Rat (Sprague-Dawley) 12–14F	10 week premating throughout gestation and lactation (F)	0, 0.5, 5, 50	BW, BC, HE, DX	Bd wt	50			
					Hemato	50			
					Develop		50		Decreased litter size
Jekat et al. 1994									**Tech (85-90% pure)**
26	Rat (Wistar) 8F	28 days (G)	0, 3, 30	BW, OW, BC	Endocr		3		Decreased serum free T4 (50%) and TSH (30%) levels and serumT4:T3 ratio (60%); decreased serum T3 (50%) and free T3 (55%) levels at 30 mg/kg/day

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Kimbrough and Linder 1978									**Tech (85% pure)**
27	Rat (Sherman) 10M, 10F	8 months (F)	M: 0, 1, 6, 32 F: 0, 1, 7, 48	BW, OW, FI, GN, HP, CS, BI	Bd wt	6 M	32 M		Decreased body weight in males at 32 mg/kg/day (15%) and females at 48 mg/kg/day (17%)
					Resp	32 M			
					Cardio	32 M			
					Hepatic		1[c]		Centrilobular hepatocyte hypertrophy in males and females at ≥1 mg/kg/day and periportal fibrosis at 32/48 mg/kg/day
					Repro	32 M			
Kimbrough and Linder 1978									**Pure (>99%)**
28	Rat (Sherman) 10M, 10F	8 months (F)	M: 0, 1, 6, 36 F: 0, 1, 7, 45	BW, OW, FI, GN, HP, CS, BI	Bd wt	6 M	36 M		10% decreased body weight in males at 36 mg/kg/day and females at 45 mg/kg/day
					Resp	36 M			
					Cardio	36 M			
					Gastro	36 M			
					Hepatic	6 M	36 M		Centrilobular hepatocyte hypertrophy in males at 36 mg/kg/day and females at 45 mg/kg/day
					Renal	36 M			
					Endocr	36 M			
					Repro	36 M			
Knudsen et al. 1974									**Tech (purity not reported)**
29	Rat (NS) 10M, 10F	12 weeks (F)	M: 0, 1.5, 3, 12 F: 0, 2.4, 4.8, 19	BW, OW, FI, GN, HP, BC, BI, OF	Bd wt	12 M			
					Resp	12 M			
					Cardio	12 M			
					Gastro	12 M			
					Hemato	19 F			
						1.5 M	3 M		Decreases in hemoglobin and RBC levels in males

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Hepatic	19 F			
						1.5 M	3 M		Centrilobular vacuolization in males
					Renal	2.4 F	4.8 F		Decreased calculi at corticomedullary junction in females
						12 M			
					Endocr	12 M			
					Neuro	12 M			
					Repro	12 M			
NTP 1999; Chhabra et al. 1999									**Pure (99%)**
30	Rat (Fischer-344) 10M, 10F	28 days (F)	0, 20, 40, 75, 150, 270	BW, CS, FI, GN, HP, OW	Death			270	3/20 animals died
					Bd wt	75		150	35 and 70% decrease in body weight gain in males and females, respectively; weight loss at 270 mg/kg/day
					Resp	270			
					Cardio	270			
					Gastro	270			
					Musc/skel	270			
					Hepatic	20 M	40 M		Increased liver weight and incidence of hepatocyte degeneration in males ≥40 mg/kg/day and in females at ≥75 mg/kg/day
					Renal	270			
					Endocr	270			
Schwetz et al. 1978									**EC-7 (90.4% pure)**
31	Rat (Sprague-Dawley) 10M, 20F	62 days premating, during mating, gestation, and lactation (F)	0, 3, 30	BW, RX, DX	Bd wt	3 F	30 F		10% decrease in maternal body weight
						30 M			
					Develop	3		30	Decreased litter size and neonatal survival; decreased neonatal body weight and growth

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Welsh et al. 1987									**Pure (>99%)**
32	Rat (Sprague-Dawley) 20M, 20F	181 days pre-mating, during mating, and through GD 20 (F)	0, 4, 13, 43	BW, RX, DX	Bd wt	13 F		43 F	76% decrease in maternal weight gain
					Repro	43			
					Develop	4	13	43	Decreased fetal body weight and crown-rump length, increased skeletal variations; increased resorptions at 13 mg/kg/day; fetal lethality at 43 mg/kg/day
Kerkvliet et al. 1982									**Tech (86% pure)**
33	Mouse (C57BL/6) NS M	10–12 weeks (F)	0, 9, 90	CS, BW, HP, IX	Bd wt	90			
					Hepatic		90		Necrosis
					Renal	90			
					Endocr	90			
					Immuno	9	90		Altered immune response
Kerkvliet et al. 1982									**Pure (>99%)**
34	Mouse (C57BL/6) NS M	10–12 weeks (F)	0, 9, 90	CS, BW, HP, IX	Bd wt	90			
					Hepatic		90		Necrosis
					Renal	90			
					Endocr	90			
					Immuno	90			
Kerkvliet et al. 1985a									**Tech (86% pure)**
35	Mouse (B6C3F1) NS	6 weeks (F)	0, 1.8, 45	BW, OW, IX	Immuno		1.8[c]		Decreased antibody response to sRBC
Kerkvliet et al. 1985a									**Tech (86% pure)**
36	Mouse (DBA/2) 6 NS	6 weeks (F)	0, 1.8, 45	BW, OW, CS, IX	Immuno	1.8	45[c]		Decreased response to sRBC

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Kerkvliet et al. 1985b									**Tech (86% pure)**
37	Mouse (C57BL/6) 12F	8 weeks (F)	0, 20, 50, 100	BW, OW, IX	Immuno		50		Decreased lymphocyte proliferative response to alloantigen
NTP 1989									**Tech (90.4% pure)**
38	Mouse (B6C3F1) 19M, 15F	30 days (F)	M: 0, 4, 20, 100, 530, 4400; F: 0, 5, 30, 140, 640, 3600	CS, BW, BC, HE, UR, OW, HP	Death			3,600 F 4,400 M	Deaths in 14/19 males at 4,400 mg/kg/day and 7/15 females at 3,600 mg/kg/day
					Bd wt	640 F		3,600 F	Weight loss; body weights 38.5% and 28.4% in males at 4,400 mg/kg/day and females at 3,600 mg/kg/day
					Hepatic	20 M	100 M		liver lesions (cytomegaly, karyomegaly, nuclear atypia, degeneration, or necrosis) in males at 100 mg/kg/day and females at 140 mg/kg/day
					Other noncancer	100 M	530 M		Decreased body temperature in males at 530 mg/kg/day and females at 640 mg/kg/day
NTP 1989									**EC-7 (90.4% pure)**
39	Mouse (B6C3F1) 19M, 15F	30 days (F)	M: 0, 4, 20, 100, 1020, 3000; F: 0, 6, 30, 140, 850, 4000	CS, BW, BC, HE, UR, OW, HP	Death			850 F 1,020 M	Deaths in 47% males at 1,020 mg/kg/day and 20% females at 850 mg/kg/day
					Bd wt	100 M	1,020 M		13% lower terminal body weight
					Hepatic	140 F	850 F		Liver lesions (cytomegaly, karyomegaly, nuclear atypia, degeneration, or necrosis) in males at 1,020 mg/kg/day and females at 850 mg/kg/day
					Other noncancer	140 F	850 F		Decreased body temperature in males at 1,020 mg/kg/day and females at 850 mg/kg/day

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 1989									**Pure (98.6%)**
40	Mouse (B6C3F1) 19M, 15F	30 days (F)	M: 0, 4, 23, 100, 600, 3000; F: 0, 6, 30, 140, 850, 4500	CS, FI, BW, BC, HE, UR, OW, HP	Death			4,500 F 3,000 M	100% mortality in males at 3,000 mg/kg/day and females at 4,500 mg/kg/day
					Bd wt	600 M			
					Hepatic	23 M	100 M		Liver lesions (cytomegaly, karyomegaly, nuclear atypia, degeneration, or necrosis) in males at 100 mg/kg/day and females at 140 mg/kg/day
					Other noncancer	100 M	600 M		Decreased body temperature in males at 600 mg/kg/day and females at 850 mg/kg/day
NTP 1989									**Tech (90.4% pure)**
41	Mouse (B6C3F1) 25M, 10F	6 months (F)	M: 0, 50, 380, 550; F: 0, 70, 200, 760	CS, FI, BW, BC, HE, UR, OW, HP, IX, NX	Death			760 F 550 M	100% mortality in males at 550 mg/kg/day and females at 760 mg/kg/day
					Bd wt	200 F			
					Resp	550 M			
					Cardio	550 M			
					Gastro	550 M			
					Hemato	550 M			
					Musc/skel	550 M			
					Hepatic		50 M		Hepatocytomegaly, pigmentation, nuclear alterations, necrosis in males at 50 mg/kg/day and females at 70 mg/kg/day
					Renal	550 M			
					Endocr	550 M			
					Immuno		50 M		Decreased response to sRBC in males at 50 mg/kg/day and females at 70 mg/kg/day

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Neuro				Dose-related increases in motor activity and startle response were observed in male and female mice after 26 weeks of exposure; investigators did not provide dose-response data
					Repro	550 M			
NTP 1989									**EC-7 (90.4% pure)**
42	Mouse (B6C3F1) 25M, 10F	6 months (F)	M: 0, 50, 150, 330; F: 0, 64, 200, 500	CS, FI, BW, BC, HE, UR, OW, HP, IX, NX	Bd wt	150 M	330 M		Lower terminal body weights in males (13%) at 330 mg/kg/day and females (11%) at 500 mg/kg/day
					Resp	50 M	150 M		Nasal mucosal metaplasia/goblet cell hyperplasia in males at 150 mg/kg/day and females at 200 mg/kg/day
					Cardio	330 M			
					Hemato	330 M			
					Musc/skel	330 M			
					Hepatic		50 M		Hepatocytomegaly, pigmentation, nuclear alterations, necrosis in males at 50 mg/kg/day and females at 64 mg/kg/day
					Renal	330 M			
					Endocr	330 M			
					Immuno	330 M			
					Neuro				Dose-related increases in motor activity and startle response were observed in female mice after 26 weeks of exposure; investigators did not provide dose-response data
					Repro	330 M			
NTP 1989									**DP-2 (91.6% pure)**
43		6 months (F)		CS, FI, BW, BC, HE, UR,	Death			580 M	2/10 deaths
					Bd wt	380 F			

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
	Mouse (B6C3F1) 25M, 10F		M: 0, 50, 140, 580; F: 0, 70, 200, 380	OW, HP, IX, NX	Resp	380 F			
					Cardio	380 F			
					Gastro	380 F			
					Hemato	380 F			
					Musc/skel	380 F			
					Hepatic		50 M		Hepatocytomegaly, pigmentation, nuclear alterations, necrosis in males at ≥50 mg/kg/day and females at ≥70 mg/kg/day
					Renal	380 M			
					Endocr	380 M			
					Immuno	200 F	380 F[c]		Decreased response to sRBC in females at 380 mg/kg/day and 580 mg/kg/day in males
					Neuro				Dose-related increases in motor activity and startle response were observed in female mice after 26 weeks of exposure; investigators did not provide dose-response data
					Repro	380 F			

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 1989									**Pure (98.6%)**
44	Mouse (B6C3F1) 25M, 10F	6 months (F)	M: 0, 110, 230, 380; F: 0, 67, 170, 540	CS, FI, BW, BC, HE, UR, OW, HP IX, NX	Bd wt	380 M			
					Resp	230 M 540 F	380 M		Nasal mucosal metaplasia/goblet cell hyperplasia in males
					Cardio	380 M			
					Gastro	380 M			
					Hemato	380 M			
					Musc/skel	380 M			
					Hepatic		67 F		Hepatocytomegaly, pigmentation, nuclear alterations, necrosis in males at ≥110 mg/kg/day and females at ≥67 mg/kg/day
					Renal	380 M			
					Endocr	380 M			
					Immuno	380 M			
					Neuro				Dose-related increases in motor activity and startle response were observed in female mice after 26 weeks of exposure; investigators did not provide dose-response data
					Repro	380 M			
Umemura et al. 1996									**Pure (98.6%)**
45	Mouse (B6C3F1) 30M	4 weeks (F)	41, 86, 200	BC, BI, HP	Hepatic		41		Increased liver weight and severe hepatocyte swelling
Umemura et al. 2006									**Pure (98.6%)**
46	Mouse (ICR) 5M	4 weeks (F)	0, 30, 60, 120, 240	BC, OW, HP	Hepatic		30		Moderate cytoplasmic hyperplasia at ≥30 mg/kg/day; increases in serum ALT and AST and slight to moderate necrosis at ≥120 mg/kg/day

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Beard et al. 1997									**Purity not reported**
47	Mink (NS) 10F	3 weeks pre-breeding through weaning 1 time/day (F)	1	BC, BW, DX GN, HP, RX	Repro		1		Increased severity of cystic uteri, decreased acceptance of second mating, decreased birth rate
CHRONIC EXPOSURE									
NTP 1999; Chhabra et al. 1999									**Pure (99%)**
48	Rat (Fischer-344) 50M, 50F	105 weeks (F)	0, 10, 20, 30	CS, BW, FI, GN, HP	Bd wt	20	30		10 and 14% decrease in body weight gain in males and females, respectively
					Resp	30			
					Cardio	30			
					Gastro	30			
					Musc/skel	30			
					Hepatic	30 F			
						10 M	20 M		Cystic hepatocyte degeneration
					Renal	30			
					Endocr	30			
NTP 1999; Chhabra et al. 1999									**Pure (99%)**
49	Rat (Fischer-344) 60M, 60F	52 weeks followed by 52 week recovery period (F)	0, 60	CS, BW, FI, GN, HP	Bd wt		60		17 and 22% decrease in body weight gain in males and females, respectively, at end of exposure period
					Resp	60			
					Cardio	60			
					Gastro	60			
					Musc/skel	60			
					Hepatic	60 F	60 M		Centrilobular hepatocyte hypertrophy and hepatocyte cytoplasmic vacuolization (males only)
					Renal	60			

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Endocr	60			
					Cancer			60 M	Mesotheliomas and nasal squamous cell carcinomas
Schwetz et al. 1978									**EC-7 (90.4% pure)**
50	Rat (Sprague-Dawley) 25M, 25F	22–24 months (F)	0, 1, 3, 10, 30	BW, OW, FI, GN, HP, BC, CS, UR	Bd wt	10 F 30 M	30 F		12% decrease in body weight gain in females
					Hepatic		10		Elevated ALT
					Renal	30			
NTP 1989									**Tech (90.4% pure)**
51	Mouse (B6C3F1) 50M,50F	2 years (F)	M: 0, 18, 35; F: 0, 17, 35	CS, FI, BW, OW, GN, HP	Bd wt	17 F 35 M	35 F		5–13% lower body weights in females
					Resp	35			
					Cardio	35			
					Hemato		18 M		Diffuse hematopoietic cells in spleen in males at ≥18 mg/kg/day and females at 35 mg/kg/day
					Musc/skel	35			
					Hepatic		17 F		Inflammation, necrosis, pigmentation in males at ≥18 mg/kg/day and females at ≥17 mg/kg/day
					Renal	35			
					Endocr	35 F	18 M		Adrenal gland hyperplasia in males
					Repro	35			
					Other noncancer	17 F	35 F		Cystic hyperplasia in mammary gland
					Cancer			18 M	Hepatocellular adenomas and adrenal pheochromocytoma in males at ≥18 mg/kg/day; hepatocellular carcinoma, and hemangiosarcomas in the liver and spleen in males at 35 mg/kg/day

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 1989									**EC-7 (90.4% pure)**
52	Mouse (B6C3F1) 50M, 50F	2 years (F)	M: 0, 18, 37, 118; F: 0, 17, 34, 114	CS, FI, BW, OW, GN, HP	Bd wt	17 F 118 M	34 F		Decreases in body weight female mice at 34 mg/kg/day (6–12%) and 114 (17–22%) mg/kg/day
					Resp	34 F	114 F		Inflammation of nasal mucosa and focal metaplasia of olfactory epithelium in males at 118 mg/kg/day and females at 114 mg/kg/day
					Cardio	114 F			
					Gastro	114 F			
					Hemato	114 F			
					Musc/skel	114 F			
					Hepatic		17 F		Inflammation, necrosis, pigmentation in males at ≥18 mg/kg/day and females at ≥17 mg/kg/day
					Renal	114 F			
					Endocr	114 F	18 M		Adrenal gland hyperplasia in males at 18 and 37 mg/kg/day
					Repro	114 F			
					Cancer			37 M	Hepatocellular adenomas and adrenal pheochromocytoma in males at ≥37 mg/kg/day, hepatocellular carcinoma in males at 118 mg/kg/day, and hemangiosarcomas in the liver and spleen and hepatocellular adenomas in females at 114 mg/kg/day

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
EPA 1997									**Tech (90.9%)**
53	Dog (Beagle) 4M, 4F	1 year (C)	0, 1.5, 3.5, 6.5	CS, BW, FI, OP, HE, BC, UR, GN, HP	Resp	6.5			
					Cardio	6.5			
					Gastro		1.5		Lymphocytic mucosal inflammation in the stomach
					Hemato	3.5 F 1.5 M	6.5 F 3.5 M		Decreased RBC count in males at 3.5 mg/kg/day and decreased hemoglobin at 6.5 mg/kg/day; in females, decreased RBC count, hemoglobin, and hematocrit at 6.5 mg/kg/day
					Hepatic		1.5 [d]		Increases in liver weight and minimal chronic inflammation; cytoplasmic vacuolation at ≥3.5 mg/kg/day and minimal necrosis at 6.5 mg/kg/day
					Renal	6.5			
					Ocular	6.5			
					Endocr	6.5			
					Neuro	6.5			
					Repro	6.5			

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Beard and Rawlings 1998									**Purity not reported**
54	Mink (NS) F0: NS; F1: 8F, 6M; F2: 10F, 8M	3 generations (F)	1	BC, BW, CS, DX, GN, HP, RX	Bd wt	1			
					Endocr		1		Decreased serum thyroxine levels
					Repro	1			

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive an acute-duration oral MRL of 0.005 mg/kg/day; LOAEL divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).
[c]Effects are likely due to a contaminant rather than pentachlorophenol.
[d]Used to derive al chronic-duration oral MRL of 0.005 mg/kg/day; LOAEL divided by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Principal studies for the MRLs.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; B = both sexes; BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; (C) = capsule; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental effects; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; FX = fetal toxicity; (G) = gavage; (GO) = gavage in oil; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; IX= immune function; LD = lactation day; LD_{50} = dose producing 50% death; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Musc/skel = muscular/skeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NX = neurological function; NS = not specified; OF = organ function; OP = ophthalmology; OW = organ weight; RBC = red blood cell; Repro = reproductive; Resp = respiratory; RX = reproductive function; sRBC = sheep red blood cell; UR = urinalysis

Figure 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral
Acute (≤14 days)

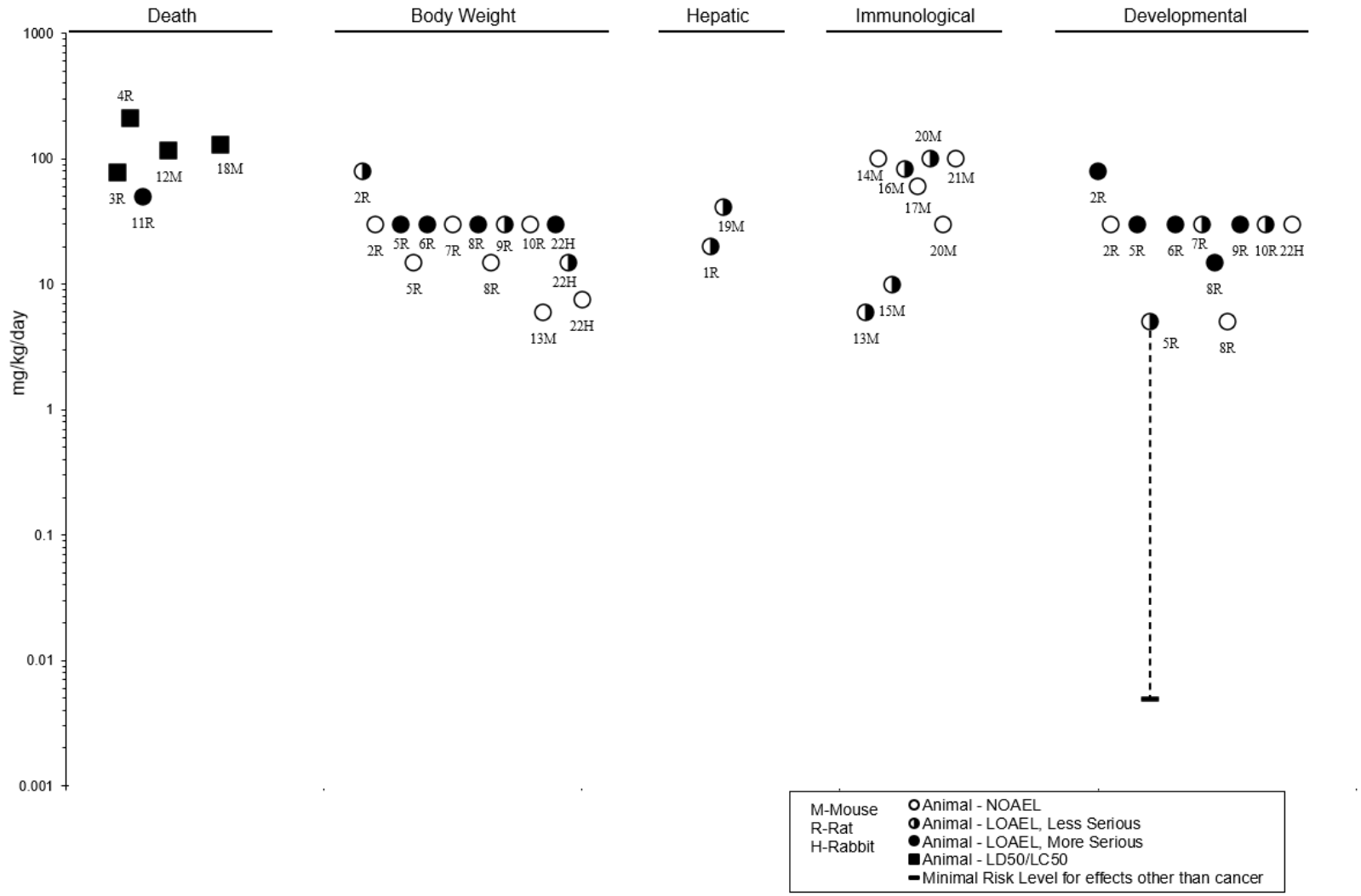


Figure 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral
Intermediate (15-364 days)

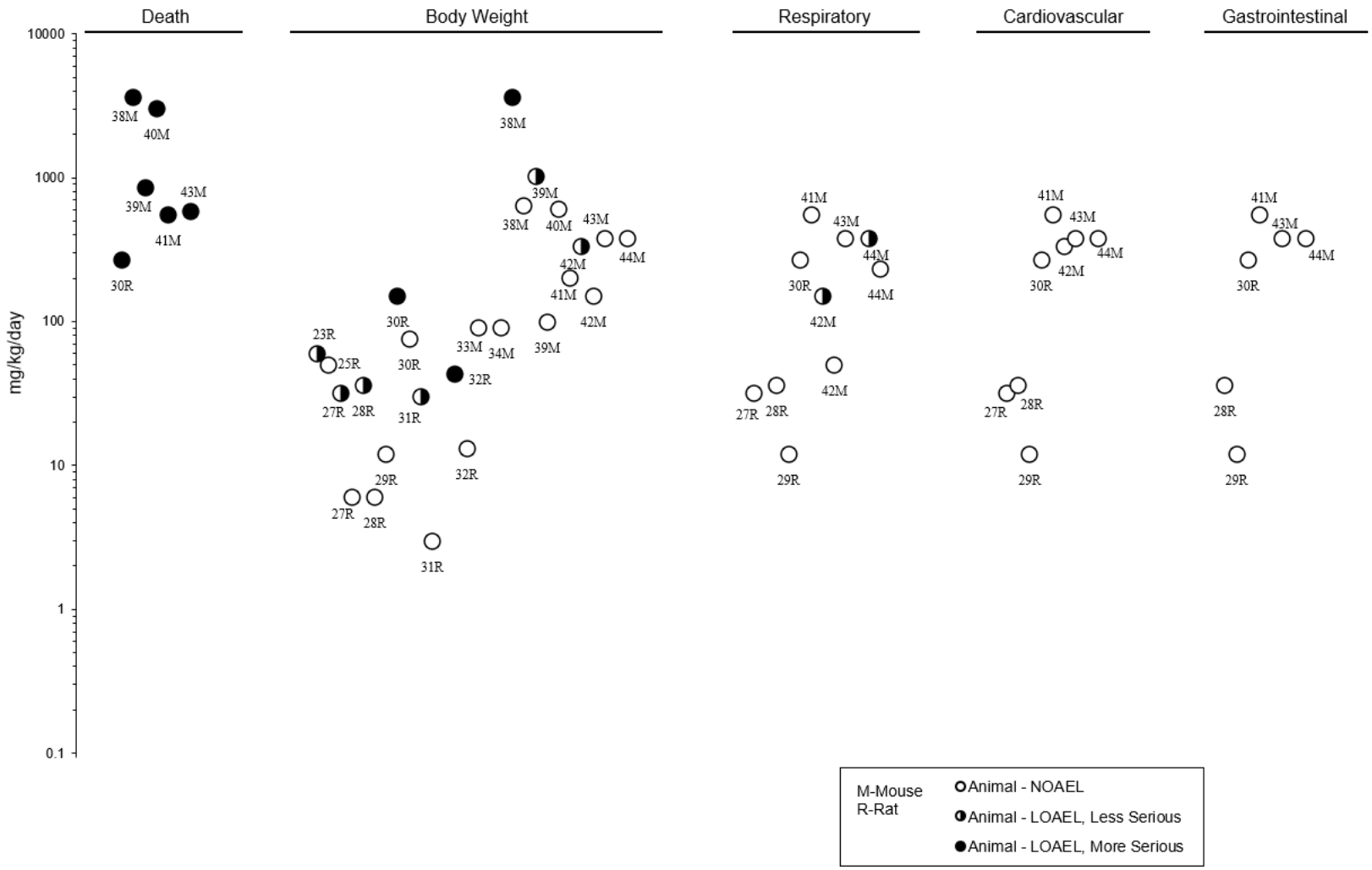


Figure 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral
Intermediate (15-364 days)

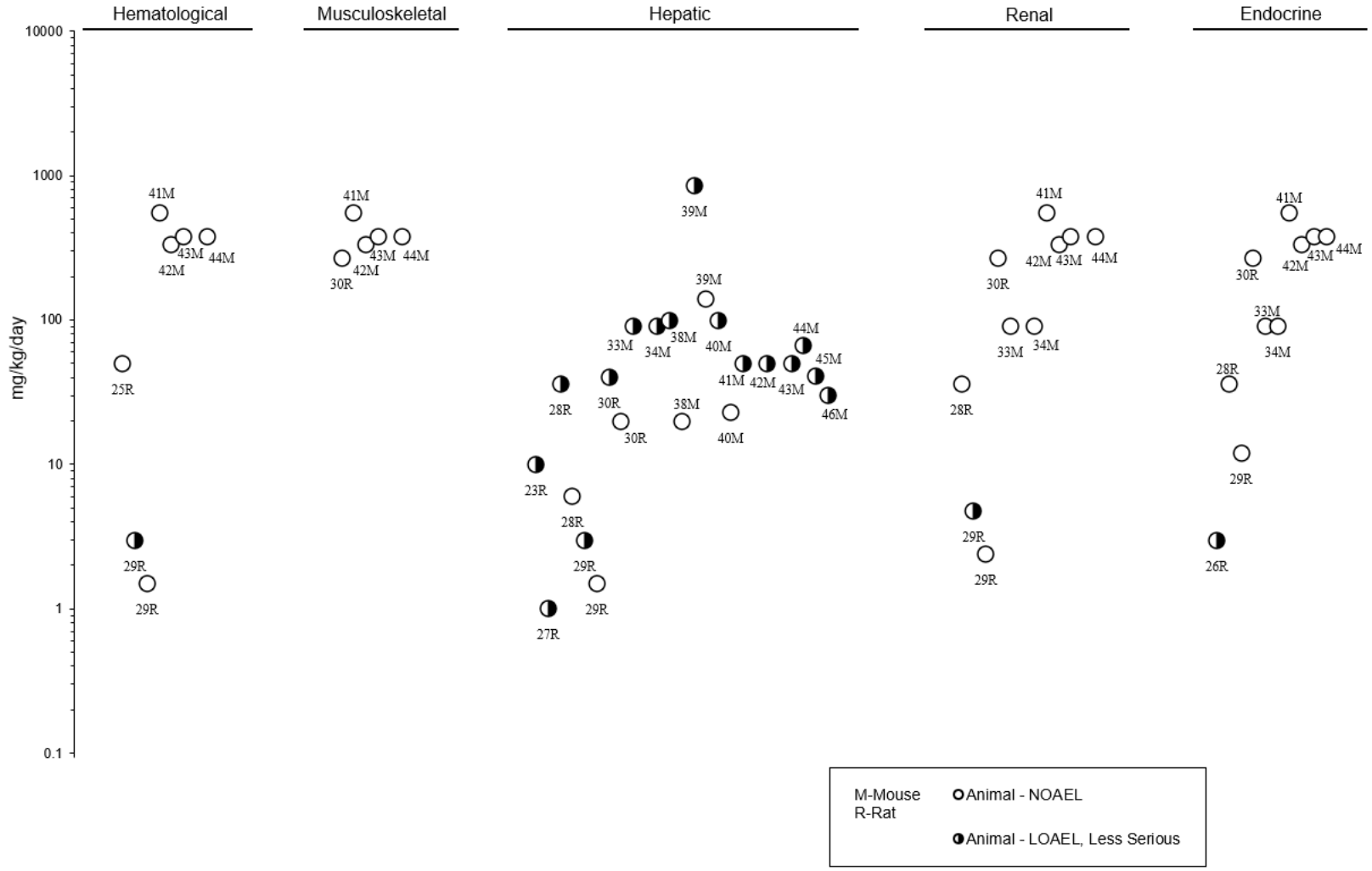


Figure 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral
Intermediate (15-364 days)

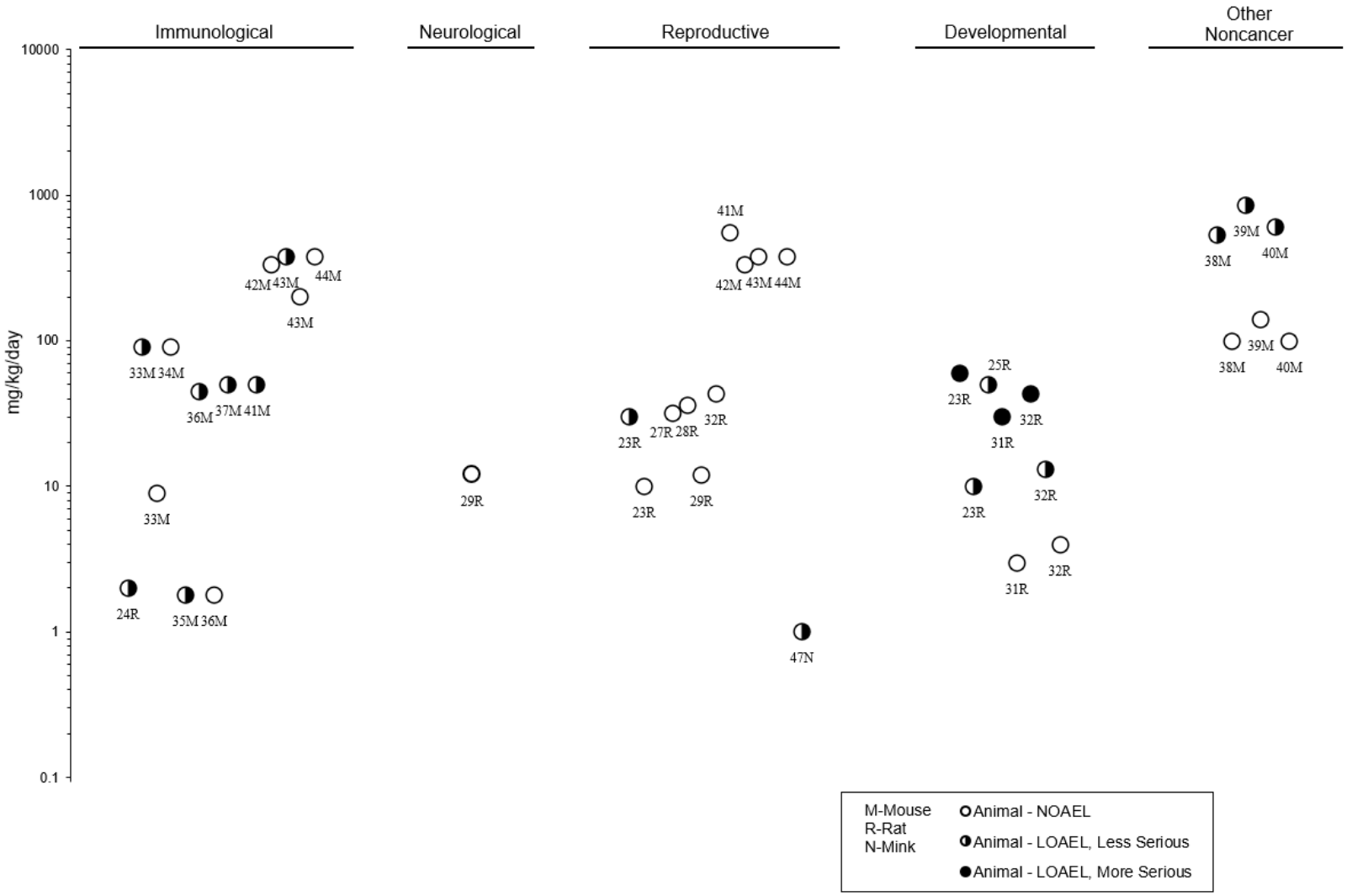


Figure 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral
Chronic (≥365 days)

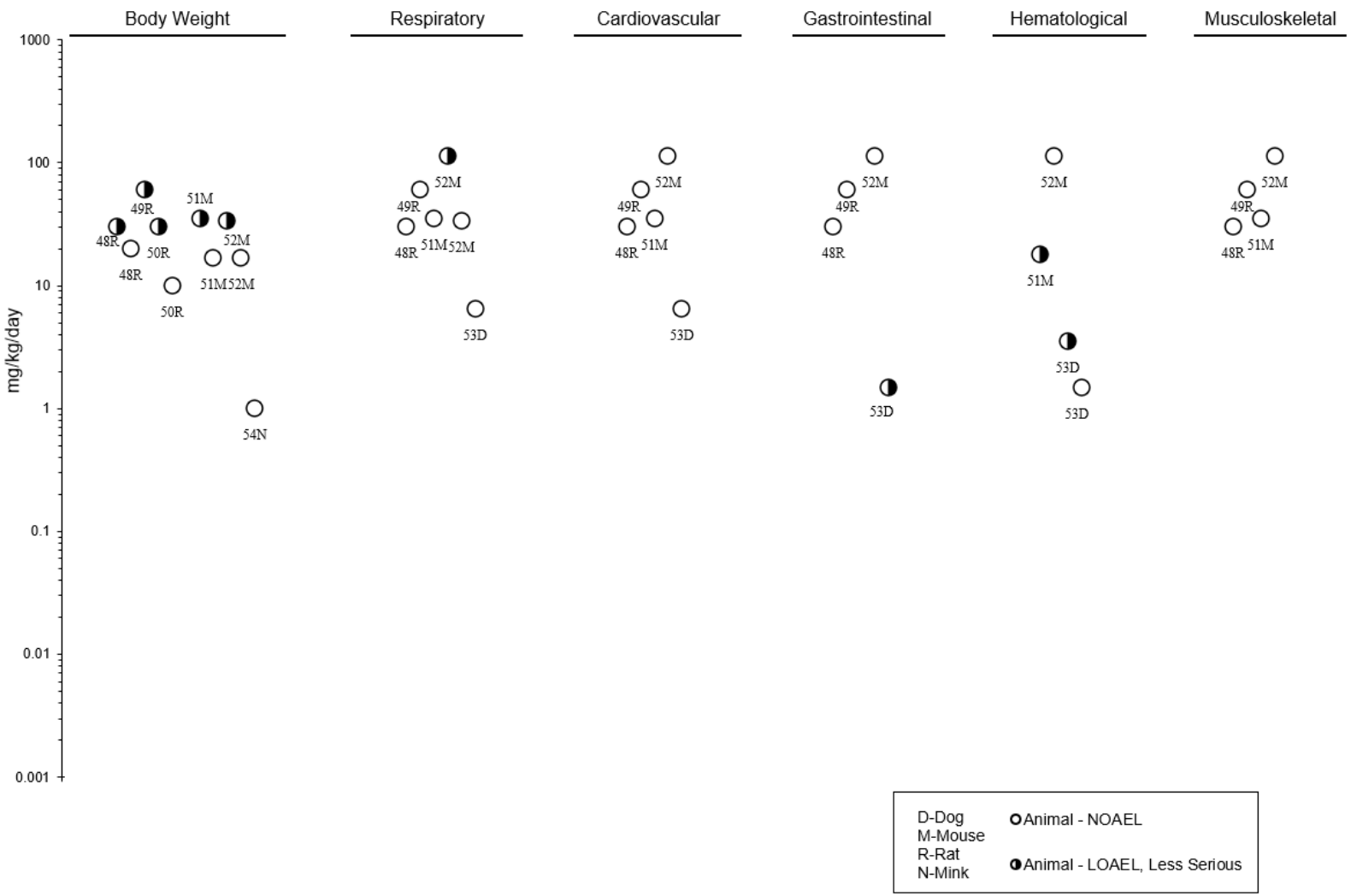
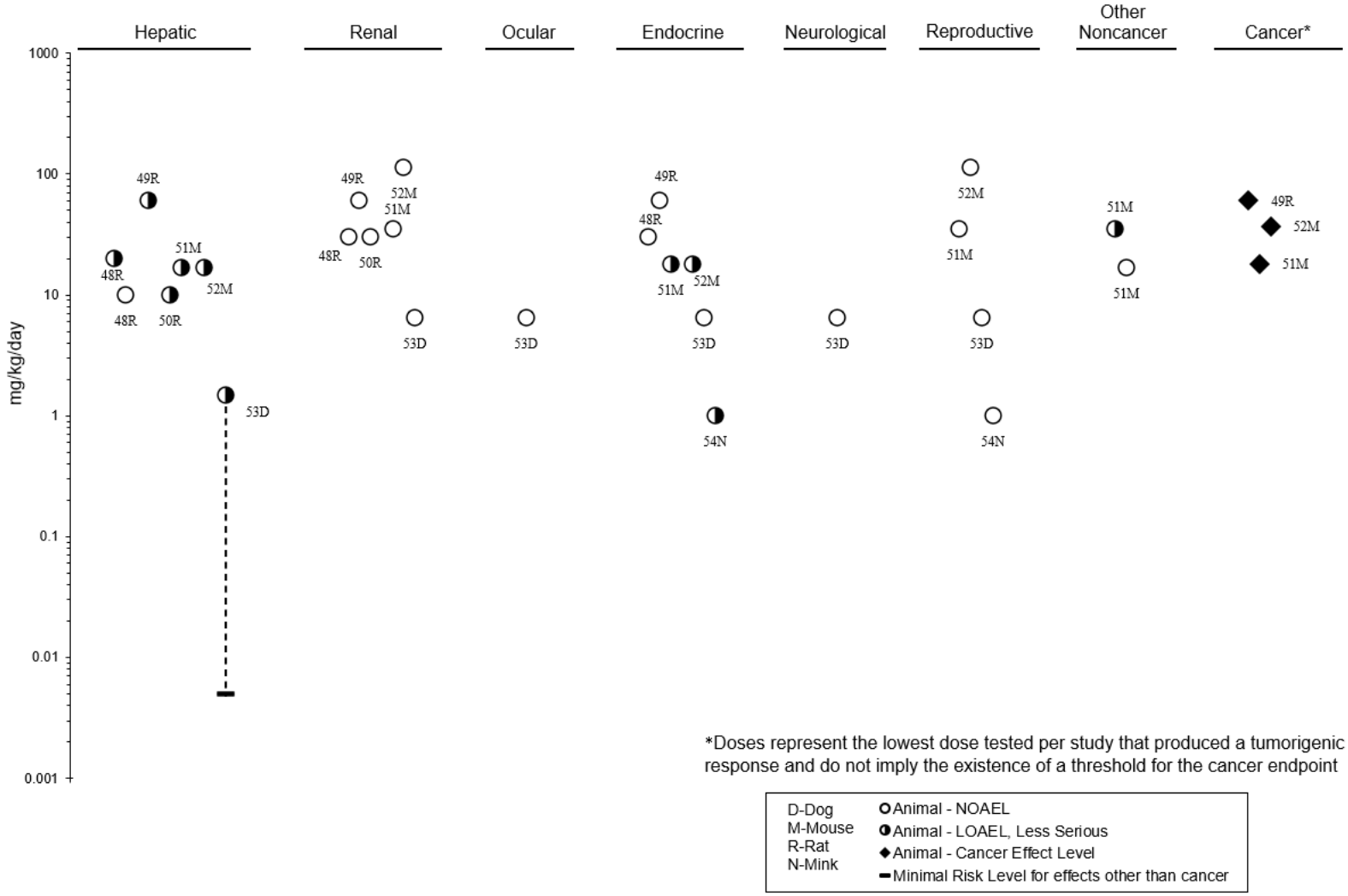


Figure 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral
Chronic (≥365 days)



2.2 DEATH

Deaths have been reported in case reports of occupational exposure to pentachlorophenol dust (Gray et al. 1985). There are also reports of mixed dermal/inhalation exposure to formulations containing pentachlorophenol (Gordon 1956; Gray et al. 1985; Roberts 1963, 1981, 1983, 1990; Smith et al. 1996). Two deaths were reported in a case report of nine newborns exposed to pentachlorophenol in a mixture of synthetic phenolic derivatives used in the hospital laundry as an antimildew agent; pentachlorophenol was found in freshly laundered diapers and in the serum and urine of the infants (Smith et al. 1996). At autopsy, both infants showed fatty metamorphosis of the liver and one showed fatty vacuolar changes in the renal tubules. Several investigators reported examining a wood preserver, herbicide sprayers, or sawmill workers with a reported cause of death of hyperthermia, which presumably resulted from the uncoupling of oxidative phosphorylation by pentachlorophenol (Bergner et al. 1965; Gray et al. 1985; Menon 1958).

Studies in laboratory animals have reported deaths after single or multiple inhalation, oral, or dermal exposures. An LC_{50} of 14 mg/m^3 was reported in rats exposed to sodium pentachlorophenate aerosol for 45 minutes (Hoben et al. 1976b). Oral LD_{50} studies have found similar values across species but did find age-related differences. The LD_{50} values of 77.9–211 mg/kg in rats (Deichmann et al. 1942; St. Omer and Gadusek 1987) and 117–177 mg/kg in mice (Borzelleca et al. 1985; Renner et al. 1986) have been reported. Pre-weaned and mature rats have been reported to have lower oral LD_{50} values for technical-grade pentachlorophenol than juvenile rats (25–50 days old) (St. Omer and Gadusek 1987). The LD_{50} values were 50, 108, 220–230, 120, and 80 mg/kg in 10-, 20-, 25–50-, 70-, and 127–134-day-old rats, respectively.

Deaths were also seen in a 30-day oral range-finding study in mice (NTP 1989), a 28-day oral range-finding study in rats with highly purified pentachlorophenol (NTP 1999), and a 6-month oral study in mice (NTP 1989). At the highest dietary concentration tested (12,500 ppm) in the 30-day study in mice (NTP 1989), incidences of deaths were higher in animals fed pure pentachlorophenol (98.6% pure with <0.0002% CDDs and CDFs) and the purified EC-7 pentachlorophenol preparation (90% pure with <0.0002% CDDs and CDFs) than in animals fed technical-grade pentachlorophenol (90% pure with 0.18% CDDs and CDFs).

One report of death following dermal exposure in experimental animals was found in the reviewed literature (Deichmann et al. 1942). Eight out of 20 rabbits administered dermal applications of 4%

pentachlorophenol (purity not indicated) in fuel oil for 6–61 weeks died of unspecified causes. The vehicle contained other known toxic substances (e.g., polyaromatic hydrocarbons), which may have contributed to the lethal effects observed.

2.3 BODY WEIGHT

In a survey of 127 current and former timber sawmill workers, Walls et al. (1998) reported increases in weight loss in workers exposed to high levels of pentachlorophenol. The workers were assigned into three exposure categories based on duration of pentachlorophenol exposure, type of work, use of personal protection, and intensity of exposure; no air monitoring data were reported.

Decreases in body weight gain have not been consistently observed in oral exposure studies in laboratory animals. Significant (10%) decreases in body weight gain were observed in several oral exposure studies in which rats or mice were administered ≥32 mg/kg/day pure pentachlorophenol, EC-7, or technical-grade pentachlorophenol for intermediate or chronic durations to rats or mice (Kimbrough and Linder 1978; NTP 1989, 1999; Schwetz et al. 1978).

Decreases in maternal body weight gain were observed in rats administered 30 mg/kg/day pure pentachlorophenol or technical-grade pentachlorophenol on gestation days (GDs) 6–15 or 8–11, but not on GDs 12–15 (Schwetz et al. 1974) or 80 mg/kg/day technical-grade pentachlorophenol on GDs 6–15 (Bernard and Hoberman 2001); or in rabbits administered 15 mg/kg/day on GDs 6–18 (Bernard et al. 2001). Decreases in maternal body weight gain were also observed in rats exposed to ≥43 mg/kg/day pure pentachlorophenol prior to mating through GD 20 (Bernard et al. 2002; Welsh et al. 1987) or to 30 mg/kg/day EC-7 prior to mating and during gestation and lactation (Schwetz et al. 1978).

2.4 RESPIRATORY

In humans, chronic high-dose occupational exposure to pentachlorophenol causes inflammation of the upper respiratory tract and bronchitis (Baader and Bauer 1951; Klemmer et al. 1980). The purity of pentachlorophenol in these cases was not specified, and inhalation of pentachlorophenol contaminants (CDDs and CDFs) and other compounds (such as dieldrin, chromium, fluorine, arsenic, copper, boron, and tin compounds) present in workplace air was likely and may have contributed to the respiratory response observed. Furthermore, the inflammation observed may have also been the result of physical irritation from the inhalation of particulate matter. A study of workers at four U.S. pentachlorophenol production facilities reported an increased risk of death from chronic obstructive pulmonary disease

(standardized mortality ratio [SMR] 1.71, 95% confidence interval [CI] 1.28–2.24) (Ruder and Yiin 2011).

In a case report, nine infants in a small nursery for newborns exhibited increased respiratory rate and labored breathing from exposure to pentachlorophenol in a mixture of synthetic phenolic derivatives in diapers and linens from the hospital laundry (Smith et al. 1996). It is likely that these effects were secondary to hyperthermia rather than a direct effect on the respiratory tract.

No animal studies evaluated potential respiratory effects following inhalation exposure to pentachlorophenol. In a 6-month dietary study (NTP 1989) with four different preparations of pentachlorophenol (technical-grade, EC-7, DP-2 formulation, and pure) in B6C3F1 mice, increased incidences of nasal mucosal metaplasia/goblet cell hyperplasia were seen in male mice exposed to 150 mg/kg/day EC-7 (90% pure) or 380 mg/kg/day pure pentachlorophenol. No significant increases were observed in female mice or in male or female mice exposed to DP-2 or technical-grade pentachlorophenol. In a chronic study, inflammation of the nasal mucosa and metaplasia of the olfactory epithelium were observed in male and female mice exposed to EC-7 in the diet at doses of 118 and 114 mg/kg/day, respectively.

No respiratory effects were observed in dietary exposure studies in rats. No alterations in the lungs were observed in rats exposed to 36 mg/kg/day pure pentachlorophenol or 32 mg/kg/day technical-grade pentachlorophenol in the diet for 8 months (Kimbrough and Linder 1978) or in the respiratory tract of rats exposed to 270 mg/kg/day pure pentachlorophenol for 28 days (NTP 1999). Chronic dietary exposure to 30 mg/kg/day pure pentachlorophenol for 2 years (NTP 1999) or 60 mg/kg/day pure pentachlorophenol for 1 year followed by a 1-year recovery period (NTP 1999) did not result in respiratory tract alterations. Similarly, no respiratory effects were observed in dogs administered technical-grade pentachlorophenol via capsules for 1 year (EPA 1997).

2.5 CARDIOVASCULAR

Tachycardia was reported in an adult male intentionally ingesting an estimated 4–8 ounces of weed killer containing 12% pentachlorophenol, 1.5% other chlorinated phenols, 82% aromatic hydrocarbons, and 4.5% inert ingredients (Haley 1977). This effect is possibly the result of pentachlorophenol's ability to uncouple oxidative phosphorylation, leading to hyperthermia and tachycardia.

One early report described the occurrence of extensive vascular damage and heart failure in rats, rabbits, guinea pigs, and dogs following a single oral administration (dose not specified) of pentachlorophenol of unidentified purity (Deichmann et al. 1942). However, most rat and mouse studies have not reported histological alterations of the heart following intermediate-duration exposure to 36–380 mg/kg/day pure pentachlorophenol (Kimbrough and Linder 1978; NTP 1989, 1999), 330 mg/kg/day EC-7 (NTP 1989), 380 mg/kg/day DP-2 (NTP 1989), or 12–550 mg/kg/day technical-grade pentachlorophenol (Knudsen et al. 1974; NTP 1989). Similarly, no cardiovascular effects were found in rats or mice exposed to 30 or 60 mg/kg/day pure pentachlorophenol (NTP 1999), 114 mg/kg/day EC-7 (NTP 1989), or 35 mg/kg/day technical-grade pentachlorophenol (NTP 1989) or in dogs administered 6.5 mg/kg/day technical-grade pentachlorophenol for 1 year (EPA 1997).

2.6 GASTROINTESTINAL

Human data on the potential gastrointestinal effects are limited to anecdotal reports of abdominal pain, nausea, and vomiting in humans occupationally exposed to pentachlorophenol of undefined purity and doses (Gordon 1956; Menon 1958).

No histological alterations were observed in gastrointestinal tissues in rats and mice exposed to pure or technical-grade pentachlorophenol, EC-7, or DP-2 in the diet for intermediate or chronic durations (NTP 1989, 1999). Lymphocytic mucosal inflammation was observed in the stomachs of dogs exposed to capsules containing ≥1.5 mg/kg/day technical-grade pentachlorophenol for 1 year (EPA 1997).

2.7 HEMATOLOGICAL

In a chronic occupational exposure study, increased numbers of immature leukocytes and basophils were observed in workers exposed to technical-grade pentachlorophenol; however, these parameters were still within normal limits (Klemmer et al. 1980). Incidents of fatal hematological disorders were found in case reports following exposure (level and duration not specified) to technical-grade pentachlorophenol or pentachlorophenol of undefined purity as a result of predominantly dermal exposure. Fifteen cases of aplastic anemia, pure red blood cell aplasia, or severe pancytopenia with abnormal marrow have been reported in individuals using pentachlorophenol-containing wood preservative products, 10 of which resulted in death (Roberts 1981, 1983, 1990). Aplastic anemia was also diagnosed in an individual using pentachlorophenol in the renovation of an old home (Rugman and Cosstick 1990). A case of intravascular hemolysis was attributed to use of an insecticide containing pentachlorophenol (Hassan et al. 1985).

Various hematologic changes of questionable biological significance have been reported in animal studies. Decreases in the number of erythrocytes, hemoglobin level, and packed cell volume were observed in rats fed technical-grade pentachlorophenol (85–90% pentachlorophenol) for 90 days; no hematological alterations were observed in rats fed pure pentachlorophenol (Johnson et al. 1973). This study provided minimal information on the study design and the results. Conflicting findings over time were reported in rats fed a purified pentachlorophenol preparation, which contained no tetrachloro-dibenzo-*p*-dioxin (2,3,7,8-TCDD) and <0.03% of the other CDDs, for 12 weeks. Increased hemoglobin and hematocrit were observed after 6 weeks of treatment, followed by a decrease in hemoglobin and erythrocytes at study termination (Knudsen et al. 1974). A decrease in white blood cell counts was observed in pigs administered purified pentachlorophenol via capsule for 30 days (Greichus et al. 1979). Decreases in erythrocyte counts were observed in dogs exposed to 3.5 mg/kg/day for 1 year; decreases in hemoglobin and hematocrit levels were observed at 6.5 mg/kg/day (EPA 1997).

No hematological alterations were observed in intermediate-duration dietary studies in which mice were exposed to 330–550 mg/kg/day pure pentachlorophenol, technical-grade pentachlorophenol, EC-7, or DP-2 (NTP 1989) or in a developmental toxicity study in which rat dams were exposed to 50 mg/kg/day (Exon and Koller 1982). In chronic-duration oral studies, diffuse hematopoietic cells were observed in the spleen of mice exposed to 18 mg/kg/day technical-grade pentachlorophenol in the diet (NTP 1989); no alterations were observed in mice exposed to 114 mg/kg/day EC-7 in the diet for 2 years (NTP 1989).

2.8 MUSCULOSKELETAL

There are limited data on potential musculoskeletal effects. No histological alterations were observed in musculoskeletal tissues in rats and mice exposed via the diet to pure pentachlorophenol (NTP 1989, 1999), technical-grade pentachlorophenol (NTP 1989), EC-7 (NTP 1989), or DP-2 (NTP 1989) for intermediate durations or to pure pentachlorophenol (NTP 1999), technical-grade pentachlorophenol (NTP 1989), or EC-7 (NTP 1989) for chronic durations.

2.9 HEPATIC

In a study of male and female pentachlorophenol-production workers, higher urinary excretion of coproporphyrins, compared with unexposed controls, was associated with workers with chloracne involved in the production of pentachlorophenol (Hryhorczuk et al. 1998). In another epidemiological

study, Cheng et al. (1993) found elevated urinary porphyrin and delta-amino levulinic acid concentrations among male workers who produced technical-grade pentachlorophenol, but there were no differences in these parameters between the workers with chloracne and those without.

No studies were located regarding hepatic effects in humans after oral exposure to pentachlorophenol. Most of the studies reviewed concerning hepatic effects of dermal exposure to pentachlorophenol in humans described case reports of individuals exposed either occupationally or in the home following the use of pentachlorophenol-containing solutions by individuals who did not employ appropriate precautionary measures. It is noted that these reports involved exposure to multiple chemicals, and it is not known if pentachlorophenol was the causative agent. Hepatic enlargement has been observed in herbicide sprayers (Gordon 1956) and in neonates exposed for a short time via contaminated diapers and bed linen in a hospital nursery (Armstrong et al. 1969; Robson et al. 1969; Smith et al. 1996). Autopsy findings in those affected individuals who died revealed fatty infiltration of the liver (in the neonates) and severe centrilobular congestion with hepatocellular fat accumulation (in the chemical worker). Centrilobular degeneration was also observed in a liver specimen from a worker who dipped wood in a preservative that contained 4.1% pentachlorophenol every day for 1 week (Bergner et al. 1965). In an epidemiologic study of male factory workers who brushed technical-grade pentachlorophenol onto wood strips, sometimes without gloves, serum biliary acid concentrations were elevated in the high-exposure group, but not the low-exposure group, as compared with controls. Exposure was assessed by measurement of pentachlorophenol concentrations in plasma and urine (Colosio et al. 1993b). Evidence of liver damage was also seen in an epidemiological study of adult males occupationally exposed to pentachlorophenol in wood-treatment plants or as farmers or pest control operators in Hawaii (Klemmer et al. 1980). This evidence consisted of elevated levels of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) following chronic, predominantly dermal exposure to technical-grade pentachlorophenol or pentachlorophenol of undefined purity.

Studies in laboratory animals provide strong evidence that the liver is a target of pentachlorophenol-induced toxicity. Evidence of biochemical (alterations in hepatic enzyme activities), gross (increased liver weight), and histopathological (hypertrophy, vacuolization, hyperplasia, fibrosis, necrosis, and degeneration) effects have been reported in acute, intermediate, and chronic oral exposure studies in rats, mice, and dogs.

At low dosages, the observed liver effects are characteristic of enzyme induction. Exposure to pure pentachlorophenol resulted in increases in liver weight, hepatocellular hypertrophy, and/or vacuolization

in mice exposed to 41 mg/kg/day for 2 weeks (Umemura et al. 1996), in rats exposed to 36 mg/kg/day for 8 months (Kimbrough and Linder 1978), in mice exposed to 30 or 41 mg/kg/day for 4 weeks (Umemura et al. 1996, 2006), and in pigs exposed to 10 mg/kg/day for 30 days (Greichus et al. 1979). Similar effects were observed following oral exposure to technical-grade pentachlorophenol in rats exposed to 1–10 mg/kg/day for an intermediate duration (Bernard et al. 2002; Kimbrough and Linder 1978; Knudsen et al. 1974) and in dogs chronically exposed to 1.5 mg/kg/day (EPA 1997). Alterations in serum ALT and/or AST were observed in rats exposed to 20 mg/kg/day methodological-grade pentachlorophenol (purity unspecified) for 2 weeks (Bekhouche et al. 2019); in mice exposed to 120 mg/kg/day pure pentachlorophenol for 4 weeks (Umemura et al. 2006), 50 mg/kg/day technical-grade pentachlorophenol for 6 months (NTP 1989), or 30 mg/kg/day for 22–24 months (Schwetz et al. 1978); and in dogs exposed to 3.5 mg/kg/day for 1 year (EPA 1997).

In general, the severity of the liver damage increased with increasing exposure concentrations. Acute-duration exposure to 20 mg/kg/day methodological-grade pentachlorophenol resulted in hepatocellular necrosis, binucleated and pyknotic hepatocytes, and dilation and congestion of the centrilobular vein and sinusoids (Bekhouche et al. 2019). Intermediate-duration exposure to doses of 7–48 mg/kg/day pure or technical-grade pentachlorophenol resulted in necrosis, periportal fibrosis, and/or hepatocellular degeneration in rats (Bernard et al. 2002; Kimbrough and Linder 1978; NTP 1999) and multifocal necrosis and hepatocellular degeneration in mice exposed to 50–90 mg/kg/day pure or technical-grade pentachlorophenol, EC-7, or DP-2 (Kerkvliet et al. 1982; NTP 1989). Hepatocellular degeneration was observed in rats exposed to 10–60 mg/kg/day pure pentachlorophenol in the diet for 52 or 104 weeks (NTP 1999). Chronic inflammation and minimal necrosis were observed at 3.5 and 6.5 mg/kg/day, respectively, in dogs administered technical-grade pentachlorophenol via capsule for 1 year (EPA 1997).

The results of the Kimbrough and Linder (1978) study suggests that the impurities found in technical-grade pentachlorophenol may influence its toxicity. The liver effects observed in this study included centrilobular hepatocyte hypertrophy at 1 mg/kg/day, periportal fibrosis at 7 mg/kg/day, and periportal fibrosis and bile duct proliferation at 48 mg/kg/day in rats exposed to technical-grade pentachlorophenol in the diet for 8 months. In contrast, minimal liver effects (centrilobular hepatocyte hypertrophy) were observed at the highest tested dose (32 mg/kg/day) of pure pentachlorophenol. It is possible that the tetrachlorophenol, hexachloro-*p*-dibenzodioxin, heptachloro-*p*-dibenzodioxin (HpCDD), octachloro-*p*-dibenzodioxin (OCDD), hexachlorodibenzofuran, pentachlorodibenzofuran, and tetrachlorodibenzofuran present in the technical-grade pentachlorophenol influenced its hepatotoxicity. However, other

studies that compared the hepatotoxicity of pure and technical-grade pentachlorophenol did not find differences in potency or the type of liver effects (Kerkvliet et al. 1982; NTP 1989).

2.10 RENAL

No studies regarding renal effects in humans after inhalation or oral exposure to pentachlorophenol were identified. Four reports were found that described renal toxic effects following dermal exposure to pentachlorophenol in humans. All involved either occupational exposure or accidental poisoning with the predominant route of exposure being dermal, but the possibility of inhalation exposure cannot be excluded. In one instance, a 3-year-old girl was exposed to pentachlorophenol of undefined composition via a pesticide-contaminated domestic water supply. Transient disruption of acid-base equilibrium and metabolic balance as evidenced by acidosis, aminoaciduria, and ketonuria suggested the occurrence of renal dysfunction in this child (Chapman and Robson 1965). In a case study of nine infants, metabolic acidosis, proteinuria, and increased blood urea nitrogen (BUN) were found following exposure of the infants to pentachlorophenol of undefined composition in diapers and bedding at a hospital that used pentachlorophenol in the hospital laundry as an antimildew agent. Fatty vacuolar changes in the renal tubules were noted in one of the two infants that died (Smith et al. 1996). An autopsy conducted on a worker who dipped wood in a preservative that contained 4.1% pentachlorophenol every day for 1 week revealed mild renal tubular degeneration (Bergner et al. 1965). Finally, evidence for pentachlorophenol-induced impaired glomerular filtration and tubular function was reported in 18 workers employed at a wood-treatment facility (Begley et al. 1977). These findings consisted of depressed creatinine clearance and phosphorus reabsorption. Considerable improvement in these symptoms was seen following a 20-day absence from work, although creatinine clearance was still depressed in 6 of the 18 workers and phosphorus reabsorption was depressed in 3 of 18 workers. These data suggest that the renal toxicant effects of technical-grade pentachlorophenol are reversible. The extent to which contaminants of technical-grade pentachlorophenol are responsible for the effects discussed above is not known. Hyperthermia may also be a mechanism of renal injury in individuals that are acutely overexposed to pentachlorophenol.

The available data from laboratory animals do not suggest that the kidney is a sensitive target of pentachlorophenol toxicity. Although a number of studies have reported increases in kidney weights, most did not find histological evidence of damage; thus, the alterations in organ weight were not considered biologically relevant. Biochemical changes indicative of renal toxicity have been reported in

pentachlorophenol-treated animals. For example, after 15 days of oral exposure to purified pentachlorophenol at 10 or 15 mg/kg/day, young pigs exhibited statistically significant increased levels of BUN, but this effect was no longer significant after 30 days of treatment (Greichus et al. 1979). Proximal tubular alkaline phosphatase activity was decreased after 1 month of twice-weekly gavage doses (40–160 mg/kg/day) of 90% pentachlorophenol (sodium salt; impurities not identified) administered to rats, but this effect was no longer evident after 3 months of treatment (Nishimura et al. 1980). The biological significance of these apparently transient renal effects with regard to long-term toxicity is not known. One study reported histological alterations: decreases in calculi at the corticomedullary junction were observed in rats exposed to 4.8 mg/kg/day technical-grade pentachlorophenol for 12 weeks (Knudsen et al. 1974). Other intermediate- and chronic-duration studies with pure, technical-grade, or commercial-grade pentachlorophenol did not report histological alterations in the kidneys (Kerkvliet et al. 1982; Kimbrough and Linder 1978; Knudsen et al. 1974; NTP 1989, 1999; Schwetz et al. 1978).

2.11 DERMAL

Occupationally-exposed workers at a wood-treatment plant exhibited a statistically significant increase in low-grade inflammation of skin and subcutaneous tissue, and severe eruptions of the skin. However, it is possible these symptoms resulted from exposure to contaminants in pentachlorophenol (e.g., CDDs, CDFs) and other materials such as dieldrin, chromium, fluorine, arsenic, copper, boron, and tin compounds (Baader and Bauer 1951; Klemmer et al. 1980). EPA (1986b) reported the presence of skin abnormalities (type not specified) in some residents of log homes treated with pentachlorophenol (purity not indicated).

Numerous occupational exposure studies have reported chloracne, characterized by extensive cysts and pus forming abscesses on the face, chest, abdomen, and proximal part of the extremities in sodium pentachlorophenate (Sehgal and Ghorpade 1983) and pentachlorophenol (Cheng et al. 1993; Hryhorczuk et al. 1998; O'Malley et al. 1990) production workers. It is likely that these workers were also exposed to CDDs and CDFs, which are known to induce chloracne in humans.

Transient localized redness and pain subsequent to immersion of the hands in a 0.4% pentachlorophenol solution for 10 minutes were exhibited by an adult male (Bevenue et al. 1967). Two cases of pemphigus vulgaris and one of chronic urticaria (both examples of severe skin lesions) attributed to nonoccupational chronic pentachlorophenol exposure (i.e., via contact with wood treated with pentachlorophenol) have

been described (Lambert et al. 1986). It is not known whether these effects were due to pentachlorophenol or from impurities.

Pentachlorophenol-induced toxic effects on the skin of experimental animals have also been reported. A single application of pentachlorophenol of unspecified purity (1,111 mg/kg in 95% ethyl alcohol or 150 mg/kg in pale paraffin oil) resulted in gross changes such as pronounced edema and inflammation leading to wrinkling, cracking, desquamation, and hair loss. Microscopic changes observed include widespread foci of atrophy and necrosis, thinning and disappearance of upper skin layers, and hyperkeratinization and hypertrophy of hair follicles (Deichmann et al. 1942). Single dermal applications of 250 mg/kg of a 10% aqueous solution of sodium pentachlorophenate of unspecified purity to rabbits did not result in dermal irritation. Repeated application of lower doses of pentachlorophenol (40 mg/kg in mineral oil) to rabbits for 21 days induced no irritation, whereas daily application of 10–50 mg/kg of a 4% solution of pentachlorophenol in fuel oil for 6–61 weeks resulted in pronounced dermal effects, and daily application of 63 mg/kg of an aqueous sodium pentachlorophenate solution for 32 days was without effect (Deichmann et al. 1942). No evidence of histologic changes in the epidermis or pilosebaceous unit were noted after application of 0.036 mg of sodium pentachlorophenate of unspecified purity to a 9 cm^2 area of the dorsal skin of hairless dogs once daily for 7 days. The toxic effects of dermal exposure to pentachlorophenol appear to be most severe following high-dose, acute exposure to pentachlorophenol in fuel oil.

Acne was observed in rabbits following application of technical-grade pentachlorophenol to the ear; acne was not observed following application of pure pentachlorophenol (Johnson et al. 1973), suggesting that the effects were due to contaminants rather than the pentachlorophenol.

2.12 OCULAR

Inflammation of the conjunctival membrane of the eyes was observed in workers exposed to technical-grade pentachlorophenol at a wood treatment plant (Klemmer et al. 1980). As discussed in Section 2.17, congenital eye cataracts were reported in the offspring of chlorophate workers (Dimich-Ward et al. 1996). No ocular alterations were observed in ophthalmologic examination of dogs administered 6.5 mg/kg/day technical-grade pentachlorophenol for 1 year (EPA 1997).

2.13 ENDOCRINE

Three human studies evaluated potential associations between pentachlorophenol exposure and thyroid disease or function. In a case-control study including 35 cases of hypothyroidism, 44 cases of hyperthyroidism, and 160 matched controls (2 controls/case), no associations were observed between blood pentachlorophenol levels and thyroid disease (Dufour et al. 2020). When analyzed together with 54 other persistent organic pollutants using a weighted quantile sum regression, pentachlorophenol was associated with lower odds for hyperthyroidism. Gerhard et al. (1998) examined several endocrine endpoints among 89 women with repeated miscarriages. An inverse correlation was found between triiodothyronine (T3) levels and pentachlorophenol levels. It should be noted that this is a preliminary study; study design limitations include (1) lack of a matched control group, (2) lack of control for other confounding factors, (3) the fact that only 15% of the women had pentachlorophenol levels that were above the reference level of 25 μg/L, (4) lack of information on possible sources of exposure to pentachlorophenol, and (5) elevated levels of other chlorinated hydrocarbons (e.g., polychlorinated biphenyls [PCBs], dichlorodiphenyltrichloroethane [DDT]) in some of the women. In another study by Gerhard et al. (1999) of a group of women with gynecological and/or endocrinological disorders, a decrease in T3 levels was found in women with elevated pentachlorophenol serum levels (median level of 3.59 μg/L); although the levels were lower than levels found in age-, geographical region-, and condition-matched controls, the mean and median T3 levels were within the normal range. An euthyroid goiter was also observed in 50% of these subjects as compared to 30% in the controls. Other statistically significant alterations in endocrine hormones included an increase in adrenocorticotropic hormone (ACTH)-stimulated cortisol levels and decreases in follicle stimulating hormone, testosterone, hydroepiandrosterone, hydroepiandrosterone sulfate, 17-hydroxypregnenolone, and 17-hydroxy-progesterone levels. As with the T3 levels, the hormone levels were within the normal range. The source of pentachlorophenol was wood ceilings that were treated with wood preservatives; it is likely that these women were also exposed to other chemicals in the wood preservative.

Significant alterations in thyroid hormone levels have been observed in laboratory animals. Gavage administration of 3 mg/kg/day pure pentachlorophenol to young adult female rats for 28 days produced decreases in serum free thyroxine (T4) levels (50%), serum thyroid stimulating hormone levels (30%), and serum T4:T3 ratio (60%) (Jekat et al. 1994). Decreases in serum T3 (50%) and free T3 (55%) were also observed at 30 mg/kg/day. In a multigeneration study in mink, significant decreases in serum T4 levels were observed in the F1 males (18%) and the F2 males (20%) and females (16%) exposed to

1 mg/kg/day pentachlorophenol (purity not reported) (Beard and Rawlings 1998). A decrease in relative thyroid weight (28%) was also observed in the F2 female mink.

Alterations in thyroid hormone levels were also observed in a series of studies in sheep. A significant decrease in T4 levels was observed in female sheep administered 2 mg/kg/day pure pentachlorophenol by gavage twice weekly for 36 days (Rawlings et al. 1998). Exposure of female sheep to 1 mg/kg/day pentachlorophenol (purity not reported) for 5 weeks premating and throughout gestation and lactation resulted in significant decreases in serum T4 levels in the mothers (Beard et al. 1999a), in the ram lambs that were also exposed for 20 weeks post weaning (Beard et al. 1999b), and in the ewe lambs also exposed for 67 weeks post weaning (Beard and Rawlings 1999). No alterations in thyroid stimulating hormone levels or the response to thyroid releasing hormone were observed in the female offspring. However, in response to thyroid stimulating hormone, there were reductions in the magnitude and duration of the T4 response and in the maximum T3 level and net T3 increase.

Studies in animals have shown that acute (single-dose, intraperitoneal injection) pentachlorophenol administration causes a marked, statistically significant decrease in serum total T4 levels in rats (van Raaij et al. 1991b). This decrease peaked 6–24 hours after administration, and T4 levels slowly returned to control values within 96 hours after administration. Further *in vitro* studies by these investigators revealed that the likely mechanism of action for this anti-thyroid effect was competition for serum protein T4 binding sites (van Raaij et al. 1991a).

Adrenal gland hyperplasia was observed in mice chronically exposed to ≥18 mg/kg/day technical-grade pentachlorophenol or EC-7 in the diet.

Other intermediate- and chronic-duration studies in rats and mice have not reported histological alterations in endocrine tissues (Kerkvliet et al. 1982; Kimbrough and Linder 1978; Knudsen et al. 1974; NTP 1989, 1999).

2.14 IMMUNOLOGICAL

In an epidemiological study, McConnachie and Zahalsky (1991) evaluated 18 lymphocyte phenotype frequencies, proliferative responses of peripheral lymphocytes to mitogens and allogenic stimulator lymphocytes, serum immunoglobulin levels, and autoantibody levels in 38 people ages 8–60 years (21 males) and 9–60 years (17 females) from 10 families who had been exposed to pentachlorophenol

(purity not indicated) in their pentachlorophenol-treated log homes for periods of 1–13 years. Fifteen of the individuals were children ages 8–18 years. The mean serum concentration of pentachlorophenol in the individuals who still lived in log homes at the time of the study was 884 μg/L; this was higher than the mean of 420 μg/L found in another study of people living in log homes and a mean level of 40 μg/L reported for members of the general public with no known exposure to pentachlorophenol (Cline et al. 1989). Comparison of the pentachlorophenol-exposed individuals with controls indicated that the exposed individuals had activated T-cells, autoimmunity, immunosuppression, and B-cell dysregulation. T-cell activation was indicated by statistically significant increases of >50% in the proportion of lymphocytes with T-cell activation markers, as detected by monoclonal antibodies, in pentachlorophenol-exposed individuals compared with controls. Autoantibodies were detected in 8 of 38 pentachlorophenol-exposed subjects, and there was increased expression of a monoclonal-antibody-detected marker associated with autoimmunity in the pentachlorophenol-exposed group. Functional immunosuppression was indicated by statistically-significant decreases of 24–41% in the proliferative response of peripheral lymphocytes of pentachlorophenol-exposed individuals, compared with controls, to three different mitogens and to allogeneic stimulation in mixed-lymphocyte culture. A statistically significant increase in natural killer cell function was also reported in pentachlorophenol-exposed women compared with women of the control group. This study is limited by the absence of reported serum pentachlorophenol concentrations in members of the control group and the lack of control for potential confounders such as smoking, hypertension, and alcohol use. Gerhard et al. (1991) reported “immunological disorders” (no further details were given) in 15 of 22 women attending a clinic for reproductive and/or endocrinological disorders. The women were exposed to pentachlorophenol by the outgassing of wood products in the home.

Two cases of pemphigus vulgaris and one of chronic urticaria (skin diseases with an immunologic etiology) have been attributed to nonoccupational exposure to pentachlorophenol (Lambert et al. 1986). Immune function was examined in 188–190 individuals exposed to pesticides containing pentachlorophenol (Daniel et al. 1995, 2001) and 32 workers treating wood with pentachlorophenol (Colosio et al. 1993b). Daniel et al. (1995) found that the likelihood of having an impaired response to at least one lymphocyte-stimulating agent was increased among individuals with blood pentachlorophenol levels of ≥10 μg/L. Impaired responses were observed in 50, 65, and 71% of subjects with blood pentachlorophenol levels of ≤10, 11–20, and >20 μg/L, respectively. In the Daniel et al. (2001) study, inverse associations were found between blood pentachlorophenol levels and several cellular and humoral immune parameters including total lymphocyte count, specific lymphocyte subpopulations (CD3+, CD4+, CD16+, CD19+, DR+, and CD4/CD8 ratio), interleukin levels (IL-2, IL-2R, IL-6, IL-10), interferon

gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and IgM-antiFab. An association was also found between pentachlorophenol blood levels and the number of impaired stimulation assays per person. Similar to the Daniel et al. (1995) study, individuals with blood pentachlorophenol levels of >10 μg/L were more likely to have blood lymphocyte counts and subpopulation counts that were below the mean level of healthy controls. In the Colosio et al. (1993b) study of workers who brushed technical-grade pentachlorophenol onto wood strips, a significant reduction in the lymphocyte response to phytohemagglutinin was observed among the highly exposed workers, as compared to controls.

A number of oral exposure studies in laboratory animals evaluated the immunotoxicity of pentachlorophenol. These studies found that exposure to technical-grade pentachlorophenol and commercial-grade pentachlorophenol affected a wide range of immune functions, such as humoral and cellular immunity, susceptibility to tumor induction, and complement activity (Holsapple et al. 1987; Kerkvliet et al. 1982, 1985a, 1985b; NTP 1989; White and Anderson 1985). Most studies of pure pentachlorophenol did not find immune effects (Kerkvliet et al. 1982, 1985a; NTP 1989), suggesting that the majority of the immunotoxic effects may be related to the level of impurities in the technical-grade product (e.g., CDDs and CDFs) (Kerkvliet et al. 1982, 1985a; NTP 1989; White and Anderson 1985). Two studies of pure pentachlorophenol reported immune effects (Blakley et al. 1998; Chen et al. 2013a). Studies that compared effects of technical-grade to pure pentachlorophenol are reviewed below in an attempt to illustrate immunotoxic effects attributable to pentachlorophenol.

Several studies evaluated effects on humoral immunity, in particular the response to sheep red blood cells (sRBC). Blakley et al. (1998) reported a decreased response to sRBC in rats administered via gavage 2 mg/kg 2 times per week for 28 days. This conflicts with the findings of Kerkvliet et al. (1985a) and NTP (1989), which found no significant alterations in the response to sRBC in mice administered pure pentachlorophenol at 60 mg/kg/day via gavage for 1–2 days or 380 mg/kg/day via the diet for 6 months, respectively. Studies of technical-grade pentachlorophenol found decreases in the response to sRBC in mice administered 10 or 83 mg/kg/day for acute durations (Holsapple et al. 1987; Kerkvliet et al. 1985a) or 1.8–50 mg/kg/day for intermediate durations (Kerkvliet et al. 1985a; NTP 1989). Studies with commercial-grade pentachlorophenol identified a higher LOAEL for impaired response to sRBC (NOAEL of 200 mg/kg/day and LOAEL of 300 mg/kg/day for mice exposed to DP-2) (NTP 1989) or did not find a significant response (NOAELs of 100 mg/kg/day [Holsapple et al. 1987] and 330 mg/kg/day [NTP 1989] in mice exposed to EC-7). A study in mice found that oral administration of 6 mg/kg pure pentachlorophenol 3 times/week for 1–2 weeks resulted in suppressed immune response to ovalbumin antigen, as evidenced by decreased levels of IgG and IgM (Chen et al. 2013a).

A series of studies conducted by Kerkvliet et al. (1985a) investigated the immunotoxicity of pentachlorophenol contaminants. Exposure to chlorinated dioxin/furan fraction isolated from technical pentachlorophenol resulted in immunosuppression; this was not seen when mice were administered the chlorinated diphenyl ethers fraction or the chlorinated phenoxyphenol fraction at doses expected to be found in technical pentachlorophenol. Co-administration of HpCDD, one of the most prevalent CDD impurities in technical-grade pentachlorophenol, with pure pentachlorophenol resulted in an immunosuppressive response that was similar in magnitude to that seen with technical-grade pentachlorophenol or HpCDD alone (Kerkvliet et al. 1985a). These results provide good evidence that impurities (particularly HpCDD) are responsible for some of the immunotoxic effects attributed to technical-grade pentachlorophenol. In another series of experiments conducted by Kerkvliet et al. (1985a), technical-grade pentachlorophenol was fed to both C57BL/6 mice and DBA/2 mice for 6 weeks. The C57BL/6 strain has a high-affinity aryl hydrocarbon (Ah) receptor and the DBA/2 strain a low-affinity Ah receptor. The ability of CDD and CDF congeners to bind to this receptor correlates with their toxicity and their ability to induce cytochrome P-450 monooxygenase activity. Antibody response to sRBC was suppressed by 28 and 72% in C57BL/6 mice exposed to 10 or 250 ppm technical-grade pentachlorophenol in the diet, as opposed to 0 and 45% in corresponding groups of DBA/2 mice. Based on these results, the investigators concluded that the immunosuppressive effect of technical-grade pentachlorophenol was probably mediated by contaminant CDDs and CDFs via interaction with the Ah receptor. This finding is supported by the results of the NTP (1989) 6-month study, which found immunosuppression in mice exposed to technical-grade pentachlorophenol or DP-2, but not in mice exposed to EC-7 or pure pentachlorophenol; EC-7 has very low levels of CDDs and CDFs, as compared to the other tested formulations.

Impurities also appear to be the causative agent for other immunological effects observed in animals exposed to technical-grade pentachlorophenol. In a test of resistance to syngeneic tumor growth, an indication of an organism's state of immunosurveillance, technical-grade pentachlorophenol induced a significant dose-independent enhancement of susceptibility to methylcholanthrene-induced sarcoma 1412 tumor growth, whereas the pure pentachlorophenol had no effect on this parameter (Kerkvliet et al. 1982). In another test of immunocompetence, an increase in mortality and secondary tumor susceptibility was observed in mice exposed to technical-grade pentachlorophenol and inoculated with Maloney sarcoma virus (MSV) to examine resistance to secondary tumor growth (Kerkvliet et al. 1982). These effects were not observed in similarly inoculated mice exposed to pure pentachlorophenol. In a third test designed to evaluate macrophage competence, resistance to encephalomyocarditis virus (EMCV), no effect was seen on susceptibility in mice exposed to technical-grade or pure pentachlorophenol (Kerkvliet et al. 1982).

The investigators concluded that immunomodulatory effects observed with pentachlorophenol were due primarily, but not exclusively, to contaminants present in the technical-grade preparation.

Studies evaluating the effect of technical-grade pentachlorophenol on T-cell, macrophage, and natural killer cell activity found that T-cell and macrophage-mediated (cell-mediated) immunocompetence is relatively resistant to technical-grade pentachlorophenol. (Kerkvliet et al. 1985b). The only statistically significant change seen was a reduction in lymphoproliferative response in mixed lymphocyte culture. This finding contrasts with marked effects that technical-grade pentachlorophenol has on antibody-mediated immunity. NTP (1989) notes that a marked effect on humoral immunity and an absence of an effect on cell-mediated immunity is also found in mice exposed to TCDD.

The complement component of the immune system in mice has also been found to be affected by exposure to technical-grade pentachlorophenol, but not EC-7 (White and Anderson 1985). In this study, technical-grade pentachlorophenol inhibited functional activity of all aspects of complement in a dose-dependent manner. This suppression was still seen up to 30 days after termination of treatment.

2.15 NEUROLOGICAL

There are limited data on the neurotoxicity of inhaled pentachlorophenol in humans. Signs of central nervous system toxicity (lethargy and tachypnea) and cerebral edema with focal swelling of the myelin sheath was observed in a worker exposed to pentachlorophenol dust (Gray et al. 1985; Walls et al. 1998). It is likely that these effects were secondary to hyperthermia, which resulted from pentachlorophenol-induced uncoupling of oxidative phosphorylation.

A study by Peper et al. (1999) examined neurotoxicity in individuals exposed to wood preserving chemicals used to treat wood ceilings and wood paneling. An increase in subjective symptoms (increased fatigue, distractibility, attenuated motivation, and depressed mood) and impaired performance on several objective tests of neurobehavioral performance (paired-associated learning with a distracting condition, verbal memory test with distraction, visual short term memory, and incidental learning of visual objects) were observed in 15 women with elevated pentachlorophenol (mean of 43.6 μg/L) and γ-hexachloro-cyclohexane (0.085 μg/L) blood levels, as compared to a sex-, age-, education-, and intelligence-matched control group. Additionally, the results of the reading speed, naming speed, paired associated learning, and visual short-term memory tests were significantly associated with pentachlorophenol blood levels. Although this study provides some suggestive evidence of the neurotoxic potential of pentachlorophenol,

interpretation of the results is complicated by co-exposure to high levels of γ-hexachlorocyclohexane (lindane) and other solvents and the small number of subjects. Sawmill workers reported an increased number of symptoms in a questionnaire assessing higher brain functions (no additional information was provided) (Walls et al. 1998); see Section 2.3 for more information on this survey study.

A reduction in median motor nerve conduction velocity was seen in male pentachlorophenol production workers, as compared to matched controls (Cheng et al. 1993). However, the reduction was only statistically significant in the subgroup of pentachlorophenol workers in the trichlorobenzene tank area where the highest levels of CDDs were also found. In contrast, Triebig et al. (1987) did not find significant alterations in motor or sensory nerve conduction velocities in the ulnar and/or median nerve in workers exposed to low levels (0.0003–0.18 mg/m^3) of technical-grade pentachlorophenol.

In a case-control study of patients with Parkinson's disease, Seidler et al. (1996) found significant associations of Parkinson's disease with long-term (>15 years) exposure to wood paneling in the home, contact with wood preservatives in free time, and contact with wood preservatives at work. However, the association of Parkinson's disease with exposure to pentachlorophenol is uncertain because the patients were more likely than control subjects to have used organochlorines and alkylated phosphates/ carbamates, and the patients reported more frequent exposure to heavy metals, solvents, exhaust fumes, and carbon monoxide than the control group.

One report describing effects of ingestion of pentachlorophenol in humans was found in the literature (Haley 1977). In this case, an adult male intentionally ingested an estimated 4–8 ounces of weed killer that contained 12% pentachlorophenol, 1.5% other chlorinated phenols, 82% aromatic petroleums, and 4.5% inert ingredients. Clinical signs observed upon subsequent hospital admission included pyrexia, diaphoresis, hyperkinesis, muscle twitching, tremors, epigastric tenderness, leg pain, tachypnea, and tachycardia. These neurologic symptoms may be the result of pentachlorophenol's ability to uncouple oxidative phosphorylation (including the resultant increase in body temperature, tachycardia, and tachypnea) rather than a direct toxic effect of pentachlorophenol on the central or peripheral nervous systems.

Numerous signs of central nervous system toxicity have been reported in case reports of individuals exposed to high levels of pentachlorophenol via dermal contact and inhalation exposure. The observed effects include intermittent delirium and convulsions (Chapman and Robson 1965) and irritability

(Robson et al. 1969; Smith et al. 1996). It is likely that these are effects secondary to hyperthermia due to pentachlorophenol-induced uncoupling of oxidative phosphorylation.

Results from animal studies demonstrate that the central nervous system is adversely affected by pentachlorophenol, possibly as a result of hyperthermia induced by uncoupling of oxidative phosphorylation. At the neurochemical level, transient changes in activity of some brain enzymes and decreased glial glutathione levels were seen in rats administered technical-grade pentachlorophenol in drinking water for 14 weeks (Savolainen and Pekari 1979). These findings suggest another biochemical component to technical-grade pentachlorophenol neurotoxicity. The possibility and extent of the role of technical-grade contaminants in producing these effects are not known, although the study authors concluded that the neurochemical changes were most likely associated with the body burden of chlorophenols. Inhibition of the uptake of T4 into the cerebrospinal fluid, as demonstrated in rats following intraperitoneal injection of pentachlorophenol, is another possible component of pentachlorophenol neurotoxicity.

A 6-month dietary study conducted by NTP (1989) reported neurobehavioral alterations in mice exposed to technical-grade pentachlorophenol, DP-2, EC-7, and pure pentachlorophenol. After 5 weeks of exposure, dose-related decreases in motor activity and rotarod performance were only observed in mice exposed to technical-grade pentachlorophenol. After 26 weeks of exposure, dose-related increases in both motor activity and startle response were observed in female mice exposed to each of the four mixtures. These alterations were also observed in male mice exposed to technical-grade pentachlorophenol. Because NTP (1989) did not provide actual dose-response data, LOAELs cannot be identified for these effects. The study did not find consistent alterations in other tests of neurotoxicity (pinna, corneal, or righting reflexes, visual placement, grip strength, or rotarod test performance).

No histological alterations were observed in the brain or spinal cord of mice exposed to 330–550 mg/kg/day technical-grade pentachlorophenol, DP-2, EC-7, and pure pentachlorophenol in the NTP (1989) 6-month study, rats exposed to 12 mg/kg/day in the 12 week study by Knudsen et al. (1974), or dogs exposed to 6.5 mg/kg/day technical-grade pentachlorophenol for 1 year (EPA 1997). Degenerative changes in 10% of the Types A and B fibers consisting of breaks in the myelin sheath of sciatic nerves and a variable loss of neurotubules, neurofilaments, and other axoplasmic components were observed in male rats administered 38 mg/kg/day pentachlorophenol (purity not reported) in drinking water for 90 days or 114 mg/kg/day for 120 days (Villena et al. 1992). Type C fibers were unaffected. These changes were more marked in the rats receiving the higher dose. No effects were observed in rats

exposed to 11.4 mg/kg/day for 60 days or 38 mg/kg/day for 60 days. While these results suggest that pentachlorophenol can cause neurotoxic changes in the morphology of peripheral nerves, since the purity of the pentachlorophenol tested was not specified, it is not possible to determine whether these changes were due to pentachlorophenol itself or impurities present in technical-grade pentachlorophenol. Other limitations associated with this study include a lack of protocol details (e.g., number of animals per group) and a lack of quantitative incidence data.

2.16 REPRODUCTIVE

In a brief report, Gerhard et al. (1991) noted that elevated blood levels of pentachlorophenol (>25 μg/L) and/or lindane (>100 ng/L) were found in 22 of 90 women with histories of habitual abortion, unexplained infertility, menstrual disorders, or the onset of menopause. Exposure duration was 4.6–10 years, and exposure occurred via off gassing (from wooden ceiling and wall panels and from carpets and leather upholstery treated with wood preservatives) as well as via dermal contact with these treated materials. Pentachlorophenol blood levels were highest in the women with infertility (mean=73 μg/L) and lower in those with menstrual dysfunction (42 μg/L). Seventeen of the 22 women also exhibited adrenocortical insufficiency, and 6 of these women had thyroid dysfunction as assessed by measurement of thyroid stimulating hormone (no further details were provided). However, a causal relationship between pentachlorophenol exposure and the effects is uncertain because of concurrent exposures to other chemicals, absence of matched controls, and lack of control for other confounding factors. Gerhard et al. (1999) also examined a group of 65 women with gynecological and/or endocrinological alterations and elevated serum pentachlorophenol levels (median level was 35.9 μg/L). Statistically significant decreases in follicle stimulating hormone and testosterone levels were found, as compared to age-, geographical-, region-, and condition-matched controls. Although the hormone levels were lower than in the control group, they were within the normal range of values. The women were exposed to pentachlorophenol via outgassing of wood ceilings treated with wood preservatives. It is likely that the women were also exposed to other components of the wood preservatives.

A second epidemiological study examined fertility in approximately 24,000 men who worked for at least 1 year in 1 of 11 sawmills (Heacock et al. 1998); the men were exposed to chlorophenates (compounds not specified) and contaminants. A decrease in fertility was observed among the chlorophenate-exposed workers, as compared to controls. However, there was no relationship between cumulative exposure and fertility when adjusted for time since first hire.

A number of animal studies have examined the reproductive toxicity of pentachlorophenol. The available data suggest that long-term exposure to technical-grade pentachlorophenol can decrease fertility. In a 2-generation study, decreased fertility (significant decreases in the number of rats mated and in the ratio of pregnant rats to the number of rats in cohabitation) was observed in the first generation of rats exposed to 60 mg/kg/day technical-grade pentachlorophenol administered by gavage (Bernard et al. 2002). No alterations in fertility were observed in the F1 generation exposed to 10 or 30 mg/kg/day or in the parental generation. The only other reproductive effects observed in this study were decreases in testicular spermatid count, decreases in absolute testes weight and the ratio of testes weight to brain weight, and focal/multifocal mononuclear cell infiltrate in the epididymis in the F1 rats administered 30 or 60 mg/kg/day. However, no alterations in the average number of motile or nonmotile sperm, epididymal or testicular sperm counts, or sperm morphology were observed in either generation. No alterations in reproductive tissues were observed in the female rats. Significant increases in the average day of preputial separation and vaginal patency were observed in the F1 generation, suggesting that *in utero* exposure to pentachlorophenol disrupted the normal development of the reproductive system. No adverse reproductive effects were observed in another multigeneration study in which mink were fed a diet containing 1 mg/kg/day pentachlorophenol (purity not reported) (Beard and Rawlings 1998). A single-generation mink study also conducted by this group reported significant decreases in the proportion of mated females accepting a second mating and the proportion of mink that whelped, although no effect on the proportion of mink that accepted the first mating or the proportion of mink with visible implantation sites were found (Beard et al. 1997). In both studies, the minks were exposed to 1 mg/kg/day pentachlorophenol (purity not reported) in the diet for 3 weeks prior to mating. Additionally, no significant alterations in mating response, ovulation rate, follicle and corpus luteum size, gestation length, pregnancy rate, lambing rate, and lamb birth rate were observed in sheep exposed to 1 mg/kg/day pentachlorophenol in the diet for 5 weeks premating and throughout the gestation and lactation periods (Beard et al. 1999a). No effect on fertility was observed in the offspring of these sheep, later mated to unexposed males (Beard and Rawlings 1999).

Several reproductive toxicity studies and general toxicity studies have reported histological alterations in reproductive tissues. Minimal to marked germinal epithelial degeneration and lack of spermatozoa in the seminiferous tubules were observed in rats exposed to 270 mg/kg/day pure pentachlorophenol in the diet for 28 days (effects may have been secondary to poor condition of animals) (NTP 1999). Effects observed in sheep include focal degeneration of the seminiferous tubules and decreased sperm density in the epididymis body (but not in caput or cauda epididymis) at 1 mg/kg/day pentachlorophenol (purity not reported) in the diet during gestation, lactation, and for 20 weeks postnatally (Beard et al. 1999b),

increased severity of oviductal intraepithelial cysts at 2 mg/kg/day pure pentachlorophenol administered by gavage twice weekly for 43 days (Rawlings et al. 1998), and lymphocyte infiltration into the endometrium at 1 mg/kg/day pentachlorophenol (purity not reported) in the diet for 5 weeks premating and during the gestation and lactation periods (Beard et al. 1999a). In mink, increased severity of cystic uterine glands was observed at 1 mg/kg/day pentachlorophenol (purity not reported) administered in the diet prior to mating and during gestation and lactation periods (Beard et al. 1997). No histological alterations in reproductive tissues were observed in male or female mice exposed to 330–550 mg/kg/day technical pentachlorophenol, DP-2, EC-7, or pure pentachlorophenol for 6 months (NTP 1989), male or female rats chronically exposed to 30 mg/kg/day pure pentachlorophenol in the diet for 2 years (NTP 1999), male or female mice exposed to technical-grade pentachlorophenol or EC-7 for 2 years (NTP 1989), or male or female dogs exposed to technical-grade pentachlorophenol for 1 year (EPA 1997). Additionally, no alterations in reproductive hormones (estradiol, testosterone, progesterone, follicle stimulating hormone, and/or luteinizing hormone levels) have been observed in mink (Beard et al. 1997) or sheep (Beard et al. 1999b).

Because no studies compared the effect on reproductive function of technical-grade pentachlorophenol and pure pentachlorophenol or did not report the purity, it is difficult to assess whether the observed reproductive effects are due to pentachlorophenol or one or more of the impurities. Studies on CDDs and CDFs have reported reproductive effects in laboratory animals, including decreases in fertility and histological alterations in the seminiferous tubules (ATSDR 1994, 1998).

2.17 DEVELOPMENTAL

Information on the developmental toxicity of pentachlorophenol in humans is limited. In a study of over 9,500 male sawmill workers exposed to chlorophenate (a mixture of the sodium salts of pentachlorophenol and tetrachlorophenol) and contaminants such as CDDs, a significant correlation between presumed exposure to chlorophenate and an increased incidence of congenital eye cataracts were observed in the workers' children (Dimich-Ward et al. 1996). Because there were no data on exposure level, exposure to chlorophenate was estimated by 10 experienced workers based on each cohort member's job title.

Several general population studies evaluated potential neurodevelopmental effects. No associations between maternal pentachlorophenol levels and cognitive and motor outcomes were observed in children 18 months of age (Meijer et al. 2008; Ruel et al. 2019) or 13–15 years of age (Berghuis et al. 2018). A

study of children 5–6 years of age found associations between maternal pentachlorophenol levels and motor, cognitive, and behavioral performance (Roze et al. 2009); it should be noted that this study also found associations with other organohalogens including brominated diphenyl ethers and PCBs.

A case-control study of 70 couples with a history of spontaneous abortions found an association between paternal blood pentachlorophenol levels and the risk of spontaneous abortions (odds ratio of 2.09, 95% confidence interval of 1.05–4.14 for 31 couples with high paternal pentachlorophenol exposure); no association was found with maternal pentachlorophenol levels (Chen et al. 2013b). An evaluation of the association between maternal pentachlorophenol levels and reproductive development in 90 mother-infant pairs found that maternal pentachlorophenol levels influenced follicle-stimulating hormone levels in boys and girls at 3 months, but no significant relationships were found with other reproductive hormone levels, testes volume, or penile length (Meijer et al. 2008). In a prospective birth cohort, no associations between maternal or child urinary levels of pentachlorophenol and body weight, height, weight-for-height, body mass index, or head circumference of children at 3 years of age (Guo et al. 2019).

A number of animal studies have examined the developmental toxicity of pentachlorophenol and provide evidence that gestational exposure can result in fetal/neonatal mortality, malformation/variations, decreased growth, and possibly functional deficits in rats exposed to pure pentachlorophenol or technical-grade pentachlorophenol. No developmental effects have been observed in rabbits administered up to 30 mg/kg/day technical-grade pentachlorophenol by gavage on GDs 6–18 (Bernard et al. 2001). Significant increases in post-implantation resorptions or embryo lethality were observed in rats administered 30 mg/kg/day pure pentachlorophenol or 15 mg/kg/day technical-grade pentachlorophenol by gavage on GDs 6–15 (Schwetz et al. 1974), in rats administered 80 mg/kg/day technical-grade pentachlorophenol by gavage on GDs 6–15 (Bernard and Hoberman 2001), and in the rats exposed to 46 mg/kg/day pure pentachlorophenol in the diet during mating and gestation (Welsh et al. 1987). An increase in the number of litters having more than two resorptions was also observed in rats exposed to 13 mg/kg/day pure pentachlorophenol (Welsh et al. 1987). Decreases in litter size and decreases in neonatal survival were observed in offspring of rats exposed for 77 days prior to gestation and throughout the gestation and lactation periods to 30 mg/kg/day EC-7 in the diet (Schwetz et al. 1978), rats exposed to 48 mg/kg/day technical-grade pentachlorophenol in the diet for 10 weeks prior to mating and throughout gestation and lactation (Exon and Koller 1982), and F1 and F2 rat pups exposed to 60 mg/kg/day technical-grade pentachlorophenol (Bernard et al. 2002).

The occurrence of malformations and variations has been reported in a small number of studies. An increase in the incidence of delayed ossification of the skull was observed in the fetuses of rats administered 5 mg/kg/day pure pentachlorophenol on GDs 6–15 (Schwetz et al. 1974). Soft tissue (subcutaneous edema) and skeletal (lumbar spurs, rib, vertebrae, and sternebrae) anomalies were observed in the offspring of rats exposed by gavage to 15 mg/kg/day of technical-grade pentachlorophenol or pure pentachlorophenol (Schwetz et al. 1974), skeletal (variations in vertebral, sternal, and pelvic ossification, increased rib pairs, delays in sternal forelimb and hindlimb ossification) and soft tissue (diaphragmatic hernia, slight to moderate dilation of the kidneys) malformations and variations have been observed in rat offspring administered 80 mg/kg/day technical-grade pentachlorophenol on GDs 6–15 (Bernard and Hoberman 2001), and skeletal variations were observed in the fetuses of rats exposed to 13 mg/kg/day pure pentachlorophenol prior to mating and through GD 20 (Welsh et al. 1987).

Decreases in growth have been reported in a number of developmental toxicity studies. Statistically significant decreases in fetal body weights were observed in the offspring of rats administered pure or technical-grade pentachlorophenol by gavage at doses of ≥30 mg/kg/day (Bernard and Hoberman 2001; Courtney et al. 1976; Larsen et al. 1975; Schwetz et al. 1974). Decreases in pup weight have been observed in the offspring of rats administered 14 mg/kg/day pure pentachlorophenol in the diet (Welsh et al. 1987), in rats in a 2-generation study administered 10 mg/kg/day technical-grade pentachlorophenol in the diet (Bernard et al. 2002), and in sheep fed 1 mg/kg/day pentachlorophenol (purity not reported) in the diet (Beard et al. 1999a).

There is some limited evidence that gestational/lactational exposure to pentachlorophenol may impair the development of the reproductive system. Significant increases in the average day of vaginal patency in F1 females exposed to 60 mg/kg/day and preputial separation in F1 males exposed to 60 mg/kg/day technical-grade pentachlorophenol (Bernard et al. 2002). Decreased fertility was also observed in the F1 generation.

Schwetz et al. (1974) examined the differences in the developmental toxicity between pure and technical-grade pentachlorophenol. The pure pentachlorophenol was slightly more toxic than the technical-grade pentachlorophenol in terms of maternal body weight gain, fetal resorptions, fetal body weight, and occurrence of fetal anomalies. The study authors estimated that the maternal dose that would be lethal to one half of the embryos was 16 mg/kg/day pure pentachlorophenol versus 44 mg/kg/day for technical-grade pentachlorophenol.

In many of the oral developmental toxicity studies, decreases in maternal body weight were observed at the same doses as the developmental effects in rats (Bernard and Hoberman 2001; Courtney et al. 1976; Schwetz et al. 1974). However, in other rat studies (Bernard et al. 2002; Welsh et al. 1987), the LOAEL for maternal toxicity was higher than the LOAEL for developmental effects (decreased fetal or pup body weight), suggesting that developmental toxicity can occur in the absence of maternal toxicity.

2.18 OTHER NONCANCER

A study of sawmill workers reported an increased incidence of nausea and fever/sweating among workers exposed to high levels of pentachlorophenol (Walls et al. 1998); see Section 2.3 for more information on this survey study.

There are limited data on the metabolic toxicity of pentachlorophenol. Nishimura et al. (1980) reported significant increases in blood glucose levels and decreases in hepatic glycogen levels in rats administered 40 mg/kg/day technical-grade sodium pentachlorophenate by gavage twice weekly for 1–3 months.

In the intermediate-duration studies conducted by NTP (1989), granular eosinophilic pigment was observed in the epithelial cells of the urinary bladder of rats exposed to technical-grade pentachlorophenol, EC-7, DP-2, and pure pentachlorophenol; the increase in pigment was not accompanied by inflammation.

2.19 CANCER

A number of epidemiological studies have evaluated the possible carcinogenicity of pentachlorophenol. Early studies conducted in the 1970s and 1980s have limited value in assessing carcinogenicity due to the use of broad occupational groups (such as wood workers or chlorophenols workers), small cohort size, follow-up periods too short to detect an excess cancer risk, mortality due to competing causes of death, and brief exposure periods. Additionally, many studies did not provide pentachlorophenol-specific exposure data. Because these studies provide limited information on the association between pentachlorophenol exposure and carcinogenicity, they are not discussed in this toxicological profile. Cohort studies (Collins et al. 2009; Demers et al. 2006; Ramlow et al. 1996; Ruder and Yiin 2011) and case-control studies (Hardell and Eriksson 1999; Hardell et al. 1994, 1995, 2002; Kogevinas et al. 1995; Pearce et al. 1986a, 1986b; Ward et al. 2009; Yang et al. 2021a) providing pentachlorophenol exposure information are summarized in Table 2-3.

Table 2-3. Summary of Select Epidemiological Studies Evaluating Possible Associations Between Cancer Outcomes and Pentachlorophenol

Reference and study population	Exposure	Measures of association (95% confidence interval)
Collins et al. 2009 Cohort study of 773 male workers at Dow manufacturing plant in Michigan; 577 of the workers had no exposure to trichlorophenol This is a follow-up to the study conducted by Ramlow et al. (1996)	Exposure estimated based on work history and historical monitoring data Worker had elevated blood levels of several hexaCDD congeners, heptaCDD, and octaCDD; 27% of the cohort developed chloracne indicating exposure to high levels of dioxins	Age and calendar year adjusted SMR (95% CI); Dow regional workers comparison group All cancers Full cohort (94 deaths): 1.0 (0.8–1.2) No trichlorophenol cohort (71 deaths): 1.0 (0.8–1.3) Non-Hodgkin lymphoma Full cohort (8 deaths): 2.4 (1.0–4.7) No trichlorophenol cohort (7 deaths): 2.8 (1.1–5.7) Kidney cancer Full cohort (4 deaths): 1.7 (0.5–4.4) No trichlorophenol cohort (4 deaths): 2.3 (0.6–5.8) Age and calendar year adjusted SMR (95% CI); Dow regional workers comparison group among workers with high cumulative exposure to CDD congeners Non-Hodgkin lymphoma 2,3,7,8-TCDD (3 deaths): 3.1 (0.6–9.1) HexaCDD (5 deaths): 5.3 (1.7–12.4) HeptaCDD (4 deaths): 4.6 (1.3–11.8) OctaCDD (4 deaths): 4.7 (1.3–12.0) TEQ (4 deaths): 4.5 (1.2–11.6)
Demers et al. 2006 Cohort study of 27,464 male sawmill workers from 14 mills in British Columbia Canada; 1,495 cancer deaths and 2,571 incident cancer cases	Exposure estimated based on detailed work history; representative exposures estimated for 3–4 time periods; dermal contact was the primary route of exposure.	Adjusted SIR values (adjusted for age and calendar period). Non-Hodgkin lymphoma incidence (92 cases): 0.99 (0.81–1.21) Multiple myeloma incidence (25 cases): 0.80 (0.52–1.18), Kidney cancer deaths (79 cases): 1.10 (0.88–1.38) See Table 2-4 for dose-response analysis data

Table 2-3. Summary of Select Epidemiological Studies Evaluating Possible Associations Between Cancer Outcomes and Pentachlorophenol

Reference and study population	Exposure	Measures of association (95% confidence interval)
Hardell and Eriksson 1999 Case-control study of Swedish males; 404 cases of non-Hodgkin lymphoma and 741 controls	Self-reported work history	Non-Hodgkin lymphoma Mostly pentachlorophenol exposure (55 cases, 87 controls): OR 1.2 (0.7–1.8)
Hardell et al. 1994 Case-control study of Swedish males; 105 cases of non-Hodgkin lymphoma and 335 controls	Self-reported work history	Non-Hodgkin lymphoma Mostly pentachlorophenol exposure (15 cases, 9 controls): OR 8.8 (3.4–24)
Hardell et al. 1995 Meta-analysis of four case-control studies conducted in Sweden (Eriksson et al. 1981, 1990; Hardell and Eriksson 1999; Hardell and Sandström 1979); total of 434 cases and 948 controls, all males	Self-reported work history	Soft tissue sarcoma Pentachlorophenol workers: OR 2.8 (1.5–5.4)
Hardell et al. 2002 Pooled data from Hardell and Eriksson (1999) and Hardell et al. (1994); 404 cases and 741 controls for non-Hodgkin lymphoma and 111 cases and 400 controls with hairy cell lymphoma, for a total of 515 cases and 1,141 controls	Self-reported work history	Non-Hodgkin lymphoma and hairy cell lymphoma (combined) Pentachlorophenol exposure (64 cases and 101 controls): OR 1.40 (0.99–1.98)

Table 2-3. Summary of Select Epidemiological Studies Evaluating Possible Associations Between Cancer Outcomes and Pentachlorophenol

Reference and study population	Exposure	Measures of association (95% confidence interval)
Kogevinas et al. 1995 Nested case control study of European workers involved in phenoxy herbicide or chlorophenols production and spraying; 32 cases and 158 controls	Company records of job histories; cumulative exposure estimated based on estimated level of exposure and duration of exposure	Non-Hodgkin lymphoma All pentachlorophenol workers (3 cases, 9 controls): OR 2.75 (0.45–17.00) High cumulative pentachlorophenol exposure (lagged 5 years) (3 cases, 5 controls): OR 4.19 (0.59–29.59)
Pearce et al. 1986a Case control study of New Zealand males; 76 cases with multiple myeloma and 315 controls with other cancer types	Self-reported work history	Multiple myeloma Ever worked as a fencer (29 cases, 87 controls) OR 1.6 (0.9–2.7)
Pearce et al. 1986b Case control study of New Zealand males; 83 cases with non-Hodgkin lymphoma and 168 controls with other cancer types	Self-reported work history	Non-Hodgkin lymphoma Ever exposed to fencing as a farmer (33 cases, 43 controls) OR 1.9 (90% CI 1.1–3.0) Ever worked as a fencing contractor (4 cases, 6 controls) OR 1.4 (90% CI 0.5–4.3) All fencing work (37 cases, 49 controls) OR 2.0 (90% CI 1.3–3.0), p=0.01

Table 2-3. Summary of Select Epidemiological Studies Evaluating Possible Associations Between Cancer Outcomes and Pentachlorophenol

Reference and study population	Exposure	Measures of association (95% confidence interval)
Ramlow et al. 1996 Cohort study of 770 male workers at Dow manufacturing plant in Michigan	Exposure estimated based on work history and historical monitoring data	Age and calendar year adjusted (95% CI); Dow regional workers comparison group Any pentachlorophenol exposure All lymphopoietic cancers (7 cases): SMR 1.4 (0.56–2.88) Other and unspecified lymphopoietic cancers (5 cases): SMR 2.0 (0.65–1.67) High cumulative exposure (0-year lag) All lymphopoietic cancers (6 cases): RR 1.91 (0.86–4.24), trend p=0.23 Other and unspecified lymphopoietic cancers (3 cases): RR 2.58 (0.98–6.80), trend p=0.08 Kidney cancer (3 cases): RR 4.16 (1.43–12.09), trend p=0.03 High cumulative exposure (15-year lag) All lymphopoietic cancers (4 cases): RR 2.01 (0.90–4.45), trend p=0.19 Kidney cancer (3 cases): RR 4.27 (1.47–12.39), trend p=0.03
Ruder and Yiin 2011 Cohort mortality study of 1,402 workers at four U.S. pentachlorophenol production facilities (excludes workers at these facilities exposed to trichlorophenol contaminated with 2,3,7,8-TCDD)	Exposure estimated from work histories	Mortality rates compared to the U.S. population All cancers (238 cases): SMR 1.25 (1.09–1.42) Respiratory cancer (105 cases): SMR 1.59 (1.30–1.92) Trachea, bronchus, lung cancer (99 cases): SMR 1.56 (1.27–1.90) Kidney cancer (4 cases): SMR 0.90 (0.25–2.31) Non-Hodgkin lymphoma (9 cases): SMR 1.41 (0.64–2.67) Multiple myeloma (6 cases): SMR 1.84 (0.68–4.00)

Table 2-3. Summary of Select Epidemiological Studies Evaluating Possible Associations Between Cancer Outcomes and Pentachlorophenol

Reference and study population	Exposure	Measures of association (95% confidence interval)
Ward et al. 2009 Case control study of 184 children (0–7 years of age) in California with acute lymphocytic leukemia and 212 matched controls	Children exposed to carpet dust containing six PCB congeners, α- and γ-chlordane, *p,p′*-DDT, *p,p′*-DDE, methoxychlor, and pentachlorophenol Geometric mean pentachloro-phenol concentration in carpet dust was 77.0 ng/g; arithmetic mean was 199.27 ng/g	Acute lymphocytic leukemia (adjusted for age, sex, race/ethnicity, age of home, and breastfeeding duration) Carpet dust concentration, trend p=0.476 2nd quartile (32.2–<75.8 ng/g) (46 cases): OR 1.28 (0.68–2.40) 3rd quartile (75.8–<164.7 ng/g) (47 cases): OR 1.46 (0.78–2.74) 4th quartile (164.7–22,676 ng/g) (31 cases): OR 0.84 (0.43–1.65) Chemical loading[a], trend p=0.045 2nd quartile (32.7–<82.2 ng/g) (50 cases): OR 0.56 (0.29–1.08) 3rd quartile (82.2–<272.5 ng/g) (50 cases): OR 0.78 (0.42–1.47) 4th quartile (≥272.5 ng/g) (50 cases): OR 0.47 (0.24–0.92)
Yang et al. 2021b, 2021c Case control study of 297 cases of thyroid cancer in China and 297 matched controls	Median urinary pentachlorophenol concentration (μg/g creatinine): Cases: 0.62 Controls: 0.39	Risk of thyroid cancer, trend p=0.008 (males p<0.001; females p=0.055) 2nd quartile (0.18–<0.40 μg/g) (60 cases): OR 1.36 (0.72–2.59) 3rd quartile (0.40–<0.95 μg/g) (88 cases): OR 2.46 (1.30–4.64) 4th quartile (≥0.95 μg/g) (111 cases): OR 3.30 (1.71–6.36) Risk of non-metastatic thyroid cancer, trend p=0.060 2nd quartile (0.18–<0.40 μg/g) (35 cases): OR 2.26 (0.82–6.22) 3rd quartile (0.40–<0.95 μg/g) (46 cases): OR 2.98 (1.12–7.87) 4th quartile (≥0.95 μg/g) (35 cases): OR 5.11 (1.67–15.60) Risk of metastatic thyroid cancer, trend p=0.019 2nd quartile (0.18–<0.40 μg/g) (39 cases): OR 0.80 (0.30–2.12) 3rd quartile (0.40–<0.95 μg/g) (25 cases): OR 3.15 (1.18–8.40) 4th quartile (≥0.95 μg/g) (38 cases): OR 4.27 (1.68–10.86) Risk of large tumor thyroid cancer (tumor diameter >1 cm), trend p=0.034 2nd quartile (0.18–<0.40 μg/g) (44 cases): OR 1.62 (0.58–4.44) 3rd quartile (0.40–<0.95 μg/g) (36 cases): OR 2.86 (1.02–8.00) 4th quartile (≥0.95 μg/g) (50 cases): OR 3.24 (1.20–8.76)

Table 2-3. Summary of Select Epidemiological Studies Evaluating Possible Associations Between Cancer Outcomes and Pentachlorophenol

Reference and study population	Exposure	Measures of association (95% confidence interval)
		Risk of unilateral thyroid cancer, trend p=0.088 2nd quartile (0.18–<0.40 µg/g) (48 cases): OR 1.63 (0.78–3.43) 3rd quartile (0.40–<0.95 µg/g) (47 cases): OR 2.54 (1.22–5.22) 4th quartile (≥0.95 µg/g) (34 cases): OR 3.14 (1.39–7.12) Risk of multifocal thyroid cancer, trend p=0.008 2nd quartile (0.18–<0.40 µg/g) (28 cases): OR 1.16 (0.36–3.78) 3rd quartile (0.40–<0.95 µg/g) (23 cases): OR 2.32 (0.60–8.93) 4th quartile (≥0.95 µg/g) (32 cases): OR 5.12 (1.56–16.74) No association with other thyroid cancer subgroups (microcarcinoma [tumor diameter ≤1 cm], bilateral, or unifocal).

[a]Chemical loading is an estimate of the amount of pentachlorophenol per square meter of carpeting.

2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; CDD = chlorinated dibenzo-*p*-dioxin; CI = confidence interval; *p,p'*-DDE = *p,p'*-dichlorodiphenyldichloroethylene; *p,p'*-DDT = *p,p'*-dichlorodiphenyltrichloroethylene; hexaCDD = hexachlorodibenzo-*p*-dioxin; heptaCDD = heptachlorodibenzo-*p*-dioxin; octaCDD = octachlorodibenzo-*p*-dioxin; OR = odds ratio; PCB = polychlorinated biphenyl; RR = relative risk; SIR = standardized incidence ratio; SMR = standardized mortality ratio; TEQ = toxic equivalency for 2,3,7,8-TCDD, hexaCDD congeners, heptaCDD congeners, and octaCDD congeners

Table 2-4. Relative Risks for Cancer in Sawmill Workers Dermally Exposed to Pentachlorophenol

	RR (95% CI)[a]			
	1–2 Exposure-years	2–5 Exposure-years	5+ Exposure-years	Trend
Kidney cancer				
Mortality	1.33 (0.51–3.47) (n=6)	2.59 (1.22–5.49) (n=17)	2.30 (1.00–5.32) (n=12)	p=0.02
Incidence	1.03 (0.49–2.18) (n=9)	1.79 (0.99–3.24) (n=22)	1.66 (0.85–3.23) (n=16)	p=0.07
Soft tissue sarcoma				
Incidence	0.64 (0.18–2.20) (n=3)	0.18 (0.04–0.85) (n=2)		p=0.11
Non-Hodgkin's lymphoma				
Mortality	1.21 (0.46–3.15) (n=6)	2.44 (1.17–5.11) (n=18)	1.77 (0.75–4.21) (n=10)	p=0.06
Incidence	1.33 (0.70–2.52) (n=13)	1.88 (1.08–3.28) (n=24)	1.71 (0.91–3.24) (n=17)	p=0.03
Multiple myeloma				
Mortality	3.30 (0.87–12.51) (n=5)	1.58 (0.38–6.63) (n=4)	4.80 (1.39–16.54) (n=10)	p=0.03
Incidence	2.09 (0.57–7.61) (n=4)	1.30 (0.34–4.98) (n=4)	4.18 (1.36–12.9) (n=11)	p=0.02

[a]Adjusted relative risk values (adjusted for age, calendar period, and race)

CI = confidence interval; RR= relative risk

Source: Demers et al. 2006

A meta-analysis, which included the Hardell et al. (1994) and Kogevinas et al. (1995) case-control studies along with three other studies reporting probable exposure to pentachlorophenol, calculated the risk of Hodgkin disease (odd ratio [OR] 1.59, 95% CI 0.51–4.95), non-Hodgkin lymphoma (OR 2.65, 95% CI 1.33–5.27), and all lymphoma (OR 2.57, 95% CI 1.52–4.35) (Zheng et al. 2015).

Exposure to technical-grade and commercial-grade pentachlorophenol can result in concomitant exposure to a number of contaminants, particularly other chlorophenols, CDDs, and CDFs. As discussed in IARC (2019), some of the epidemiological studies (e.g., Collins et al. 2009; Demers et al. 2006) have assessed co-exposure to other chlorophenols and several CDDs and CDFs by using high-quality exposure assessment techniques, including measurement of CDD and CDF serum levels and estimation of cumulative dermal exposure to pentachlorophenol. IARC (2019) and EPA (2010) noted that the types of cancers observed in the pentachlorophenol workers (primarily non-Hodgkin lymphoma) differed from the pattern reported in epidemiological studies of persons highly exposed to dioxins (all cancers combined, lung cancer, soft tissue sarcoma, and non-Hodgkin lymphoma). Additionally, EPA (2010) noted that in

the Kogevinas et al. (1995) study, the association between non-Hodgkin lymphoma and pentachlorophenol was stronger than the associations with CDDs and CDFs. In studies of laboratory animals, the pattern of excess cancers was similar for pure pentachlorophenol, technical-grade pentachlorophenol, and commercial-grade pentachlorophenol.

Based on the results of cohort and case-control studies, HHS (NTP 2016), EPA (IRIS 2010), and IARC (2019) concluded that the available data demonstrated an association between pentachlorophenol and non-Hodgkin lymphoma. IARC (2019) considered the data sufficient to establish a causal relationship; HHS (NTP 2016) considered the data to be suggestive of a causal relationship but noted that it has not been established. Although increases in the risk of other tumor types were observed in some studies, IARC (2019) concluded that the findings for other tumor sites were inconsistent across studies. One case-control study published after the IARC (2019) report suggests an association between thyroid cancer and pentachlorophenol exposure in the general population (Yang et al. 2021b).

The carcinogenicity of pentachlorophenol has been evaluated in several oral exposure studies in rats and mice (NCI 1968; NTP 1989, 1999; Schwetz et al. 1978); these studies evaluated three grades of pentachlorophenol—pure pentachlorophenol, technical-grade pentachlorophenol, and EC-7; a study of transgenic mice also evaluated the carcinogenicity of pure pentachlorophenol (Tasaki et al. 2014). In a 2-year study conducted by NTP (1999), no significant increases in tumor incidence were observed in rats exposed to 30 mg/kg/day pure pentachlorophenol in the diet. However, in rats exposed via the diet to 60 mg/kg/day pure pentachlorophenol for 1 year followed by a 1-year recovery period, increases in the incidence of mesothelioma originating in the tunica vaginalis and nasal squamous cell carcinoma were observed in male rats (NTP 1999); no increases in tumor incidence were observed in the female rats. It is noted that the incidence of nasal carcinoma was not significantly higher than controls but did exceed the incidence in historical controls and the investigators considered them to be chemical-related. In *Nrf2*-deficient mice, dietary exposure to pure pentachlorophenol for 52 weeks resulted in increased incidences of cholangiocarcinomas and hepatocellular adenomas (Tasaki et al. 2014); no increases in tumor incidences were observed in *Nrf2* wild type mice.

Several studies evaluated the carcinogenicity of EC-7, which contains approximately 90% pentachlorophenol and 10% contaminants; 9.4% of the impurities are tetrachlorophenol (NTP 1989). In a preliminary study conducted by NCI (1968; results also reported in Innes et al. 1969), 46.4 mg/kg/day EC-7 in corn oil administered via gavage to mice for 18 months did not result in increases in the incidence of tumors. Schwetz et al. (1978) also reported no increases in tumor incidence in rats exposed

to 30 mg/kg/day EC-7 in the diet for 22–24 months. In contrast, NTP (1989) reported an increased incidence of hepatocellular adenomas and adrenal pheochromocytoma in male mice exposed to ≥37 mg/kg/day EC-7 in the diet for 2 years. Hepatocellular carcinomas were observed in males exposed to 118 mg/kg/day and hemangiosarcomas in the liver and spleen and hepatocellular adenomas were observed in female mice exposed to 114 mg/kg/day.

The carcinogenicity of technical-grade pentachlorophenol was evaluated by NTP (1989). Technical-grade pentachlorophenol was 90.4% pentachlorophenol with tetrachlorophenol, higher CDDs, CDFs, and chlorohydroxydiphenyl ethers as the primary contaminants. Increases in tumor incidences were observed in the liver, adrenal gland, and spleen. Neoplastic liver lesions included hepatocellular adenomas in male mice at ≥18 mg/kg/day and hepatocellular carcinoma in males at 35 mg/kg/day. In the adrenal gland, pheochromocytomas were observed in males in the ≥18 mg/kg/day groups. A significant increase in hemangiosarcomas in the liver and spleen (most observed in the spleen) were observed in female mice exposed to 35 mg/kg/day.

In initiation-promotion studies in mice, pure pentachlorophenol promoted diethylnitrosamine-induced intrahepatic biliary cysts to cholangiomas and cholangiocarcinomas and increased the formation of hepatocellular adenomas (Umemura et al. 1999, 2003a, 2003b). When pentachlorophenol was given as an initiator with phenobarbital, there were no increases in tumor incidence (Umemura et al. 1999).

In a dermal exposure study, a 20% solution of commercial-grade pentachlorophenol in benzene was applied to shaved skin of mice twice a week for 13 weeks. Mice were previously treated with a dose of 0.3% dimethylbenzanthracene (DMBA) in benzene to induce skin cancer (Boutwell and Bosch 1959). No increase in DMBA-induced skin tumors resulted from pentachlorophenol treatment.

In zetaglobin v-Has-ras (Tg·AC) transgenic female mice, dermal exposure to pentachlorophenol in acetone 5 days/week for 20 weeks in the diet for 26 weeks resulted in an increase in the incidence of skin papillomas in mice exposed to 1.5 or 3.0 mg (Spalding et al. 2000).

As reviewed by EPA (2010) and IARC (2019), there is evidence of several carcinogenic mechanisms of action for pentachlorophenol:

- *Oxidative stress.* Increases in reactive oxygen species, oxidative stress markers, and deoxyribonucleic acid (DNA) adducts associated with oxidative stress have been found in *in vitro* studies in human cells and mammalian cells, *in vivo* studies in laboratory animals, and non-mammalian test systems in response to exposure with pentachlorophenol or its metabolites

(tetrachlorohydroquinone [TCHQ] and tetrachlorobenzoquinone [TCBQ]). Several studies in mice have found dose- and time-related increases in 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels in the liver; the cumulative oxidative DNA damage could result in critical mutations.

- *Genotoxicity.* Genotoxic effects (e.g., chromosomal aberrations, sister chromatid exchanges, and single strand breaks) have been observed in *in vitro* mammalian cells exposed to pentachlorophenol or TCHQ. Mixed results have been found in *in vivo* studies for micronuclei formation, chromosomal aberrations, or sister chromatid exchanges in human lymphocytes or in rats or mice exposed to pentachlorophenol.
- *Modulation of receptor-mediated effects.* There are some suggestive data that pentachlorophenol can interact with several nuclear receptor subtypes including estrogen receptors and the Ah receptor.
- *Alterations in cell proliferation or death. In vitro* studies in human cell lines have demonstrated pentachlorophenol- and/or TCHQ-induced alterations in the expression of several genes relevant to apoptosis. *In vivo* mouse studies have demonstrated increased cell proliferation and inhibition of gap junction intercellular communication in hepatocytes.

HHS has categorized pentachlorophenol as "reasonably anticipated to be a human carcinogen" (NTP 2016) and EPA has categorized it as "likely to be carcinogenic to humans" (IRIS 2010). IARC (2019) concluded that pentachlorophenol is "carcinogenic to humans" (Group 1).

2.20 GENOTOXICITY

Numerous *in vivo* and *in vitro* studies have assessed the genotoxic potential of pentachlorophenol, and the results of these studies are presented in Tables 2-5 and 2-6, respectively. Three studies examined the clastogenic activity of pentachlorophenol in workers primarily exposed via inhalation. A marginal increase in chromosomal aberrations was found in the lymphocytes of workers exposed to pentachlorophenol or its sodium salt (Bauchinger et al. 1982). In contrast, studies by Wyllie et al. (1975) and Ziemsen et al. (1987) did not find significant increases in the occurrence of chromosomal aberrations in their studies of workers. The occurrence of sister chromatid exchange was not increased in the lymphocytes of workers (Bauchinger et al. 1982; Ziemsen et al. 1987). No other human *in vivo* genotoxicity studies were located. An increase in DNA adduct formation was observed in the liver of mice orally exposed to pentachlorophenol (Sai-Kato et al. 1995; Umemura et al. 1996, 2003a, 2006), but not in the kidney or spleen (Sai-Kato et al. 1995), and positive results were seen in a coat color spot test in mouse embryos treated transplacentally with pentachlorophenol (Fahrig et al. 1978). Evidence of DNA damage (increased levels of 8-oxodeoxyguanosine in the liver) was observed in rats orally exposed to 60 mg/kg/day pentachlorophenol in the diet for 27 weeks (Lin et al. 2002). However, DNA damage was not observed when the rats were exposed to a single gavage dose of 120 or 60 mg/kg/day for 5 days (Lin et al. 2002). No evidence of genotoxicity was observed in assays of sex-linked recessive lethal mutations in *Drosophila melanogaster* (Fahrig 1974; Fahrig et al. 1978; Vogel and Chandler 1974), micronuclei

formation in rats and mice (NTP 1999), and gene mutations and recombination in a mouse spot test (Fahrig and Steinkamp-Zucht 1996).

Table 2-5. Genotoxicity of Pentachlorophenol *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Drosophila melanogaster spermatocytes	Sex-linked recessive lethal mutation	–	Fahrig 1974; Fahrig et al. 1978; Vogel and Chandler 1974
Human lymphocytes (occupational exposure)	Chromosomal aberrations	(+)	Bauchinger et al. 1982
		–	Wyllie et al. 1975
		–	Ziemsen et al. 1987
	Sister chromatid exchange	–	Bauchinger et al. 1982
		–	Ziemsen et al. 1987
B6C3F1 mouse (oral exposure)	DNA adduct formation	+	Sai-Kato et al. 1995; Umemura et al. 1996, 2003a, 2006
Fischer 344 rats (oral exposure for 1 or 5 days)	DNA damage	–	Lin et al. 2002
		+	Lin et al. 2002
Mouse bone marrow (intraperitoneal exposure)	Micronuclei	–	NTP 1999
		–	NTP 1999
Mouse embryonic cells (transplacental exposure)	Gene mutation	(+)	Fahrig et al. 1978
Mouse/spot test	Gene mutation	–	Fahrig and Steinkamp-Zucht 1996
	Recombination	–	Fahrig and Steinkamp-Zucht 1996

– = negative result; + = positive result; (+) = weakly positive results; DNA = deoxyribonucleic acid

Table 2-6. Genotoxicity of Pentachlorophenol *In Vitro*

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Prokaryotic organisms				
Salmonella typhimurium	Gene mutation	–	–	Donnelly et al. 1998; EPA 1977; Kubo et al. 2002; Markiewicz et al. 1996; Moriya et al. 1983; NTP 1999; Waters et al. 1982
S. typhimurium/spot test	Gene mutation	NT	–	Andersen et al. 1972; Lemma and Ames 1975
S. typhimurium (mouse host-mediated assay)	Gene mutation	–	NT	Buselmaier et al. 1973
Escherichia coli/spot test	Gene mutation	NT	–	Waters et al. 1982
Serratia marcescens/spot test	DNA damage	NT	–	Fahrig 1974

Table 2-6. Genotoxicity of Pentachlorophenol *In Vitro*

Species (test system)	Endpoint	Results		Reference
		Activation		
		With	Without	
Bacillus subtilis/rec- assay	DNA damage	NT	+	Waters et al. 1982
E. coli pol A	DNA damage	NT	–	Waters et al. 1982
Eukaryotic organisms				
Saccharomyces cerevisiae MP-1	Gene mutation	NT	+	Fahrig et al. 1978
S. cerevisiae aAeZ	Recombination	NT	+	Fahrig 1974
S. cerevisiae MP-1/ intergenic recombination	Recombination	NT	–	Fahrig et al. 1978
S. cerevisiae MP-1/ intergenic recombination	Recombination	NT	+	Fahrig et al. 1978
S. cerevisiae	Recombination	+	+	Waters et al. 1982
Mammalian cells				
Human lymphocytes	Chromosomal aberrations	NT	(+)	Fahrig 1974
Human lymphocytes	DNA damage (single strand breaks)	NT	+	Maheshwari and Mahmood 2020a
Human lymphocytes	DNA damage (single strand breaks)	NT	+	Maheshwari and Mahmood 2020b
Chinese hamster ovary cells	Chromosomal aberrations	(+)	–	NTP 1999
Chinese hamster ovary cells	Sister chromatid exchange	–	(+)	NTP 1999
Human nasal mucosal cells	DNA damage	NT	+	Tisch et al. 2005
Chinese hamster ovary cells	DNA damage	NT	–	Ehrlich 1990
Chinese hamster V79 cells	DNA damage (8-OH-dG adduct)	NT	–	Dahlhaus et al. 1996
Chinese hamster V79 cells	DNA damage (single-strand breaks)	NT	–	Dahlhaus et al. 1996
Mouse embryonic fibroblast cells	DNA damage (single-strand breaks)	(+)	–	Wang and Lin 1995
Chinese hamster ovary cells	DNA repair defect	NT	–	Johansson et al. 2004

+ = positive results; (+) = weakly positive results; – = negative results; DNA = deoxyribonucleic acid; NT = not tested

No alterations in the occurrence of gene mutations (Andersen et al. 1972; Donnelly et al. 1998; EPA 1977; Lemma and Ames 1975; Markiewicz et al. 1996; Moriya et al. 1983; NTP 1999; Waters et al. 1982) or DNA damage (Fahrig 1974; Waters et al. 1982) were observed in bacterial systems, with the exception of one study that reported positive activity in the rec assay using *Bacillus subtilis* (Waters et al. 1982). In yeast, pentachlorophenol induced gene mutations (Fahrig 1974; Fahrig et al. 1978) and genetic recombination (Fahrig et al. 1978; Waters et al. 1982). Weak clastogenic activity was observed in

chromosomal aberration assays in human lymphocyte (Fahrig 1974) and in chromosomal aberration and sister chromatid exchange assays in Chinese hamster ovary cells (NTP 1999). No significant increases in the occurrence of DNA damage (adduct formation or single-strand breaks) were seen in mouse and hamster cell lines (Dahlhaus et al. 1996; Ehrlich 1990; Wang and Lin 1995); however, increased DNA damage was observed in human nasal mucosal cells (Tisch et al. 2005) and lymphocytes (Maheshwari and Mahmood 2020a, 2020b).

2.21 MECHANISMS OF ACTION

It is widely believed that pentachlorophenol exerts its toxic effects, at least in part, by uncoupling mitochondrial oxidative phosphorylation, thereby causing accelerated aerobic metabolism and increased heat production. Pentachlorophenol has been found to bind to purified rat liver mitochondrial protein. This may induce conformational changes in enzymes involved in oxidative phosphorylation (Weinbach and Garbus 1965). The pattern of pentachlorophenol-induced toxicity often seen in humans and animals supports this proposed mechanism of action. A young worker who died following 3 weeks of exposure to pentachlorophenol dust in a chemical plant was found to have cerebral edema and fatty degeneration of liver and lungs at autopsy (Gray et al. 1985). The study authors concluded that these clinical findings are consistent with a hypermetabolic state resulting from a derangement of aerobic metabolism and characterized by hyperthermia, which can lead to tachycardia, tachypnea, hyperemia, diaphoresis, and metabolic acidosis. This is usually followed by death and rapid, profound rigor mortis. Toxicity resulting from uncoupling of oxidative phosphorylation was generally seen prior to death in animals acutely exposed to pentachlorophenol. These included accelerated respiration, hyperemia, cardiac and muscular collapse, asphyxial convulsions, death, and rapid rigor mortis (St. Omer and Gadusek 1987). The ultrastructural changes observed in mitochondria from liver cells of rats treated with technical-grade pentachlorophenol for 15 days are consistent with uncoupling of oxidative phosphorylation (Fleischer et al. 1980).

The cell membrane is apparently a possible site of action for pentachlorophenol. Lipid bilayers of purified and total cell membranes have been reported to destabilize following sublethal pentachlorophenol treatment (Duxbury and Thompson 1987). This was evidenced by a 50% decrease in bulk lipid fluidity attributable to disruption of the bilayer by pentachlorophenol. These authors also found that pentachlorophenol partitions into the hydrophobic interior of the bilayer. Other membrane changes observed by these investigators included a decrease in phospholipid phosphate levels that they believe was a result of a

selective chemical effect on phospholipase C. However, the authors concluded that this was only a sublethal effect since the cells remained viable.

In another investigation of the physicochemical basis of pentachlorophenol membrane effects, membrane toxicity was associated with the pentachlorophenol-induced change in hydrogen ion permeability of the membrane lipid matrix (Smejtek 1987). The onset of toxic effects was correlated with the loss of membrane electrical resistance and a measurable amount of pentachlorophenol binding to the membrane. In human neuroblastoma cells and lymphocytes, *in vitro* exposure to pentachlorophenol or its metabolites, TCBQ and TBHQ, reduced mitochondrial membrane potential, resulting in mitochondrial dysfunction (Fraser et al. 2019; Maheshwari and Mahmood 2020a). These changes were accompanied by oxidative stress (e.g., increased reactive oxidant species, decreased antioxidant enzymes) followed by apoptosis, lysis, and/or necrosis of cells. Fraser et al. (2019) concluded that since mitochondrial dysfunction was observed sooner than oxidative stress, it was a precursor event. However, oxidative stress, heme degradation, and hemolysis were also observed in red blood cells, which lack mitochondria (Maheshwari and Mahmood 2020a, 2020b; Maheshwari et al. 2019)

Studies described above indicate that pentachlorophenol can disrupt membrane structure and function. These effects could conceivably occur throughout the body and could therefore explain the wide range of toxic effects associated with pentachlorophenol, including the uncoupling of oxidative phosphorylation.

Oral and intraperitoneal administration of pentachlorophenol to animals causes adverse effects on thyroid homeostasis (e.g., decreased serum T4) and on the thyroid gland (Beard and Rawlings 1998; Beard et al. 1999a; Jekat et al. 1994; van Raaij et al. 1991b). These effects may occur during gestation, pregnancy, and lactation (Beard and Rawlings 1998; Beard et al. 1999a). Further *in vitro* studies by van Raaij et al. (1991a) revealed that the likely mechanism of action for this anti-thyroid effect of pentachlorophenol was competition for serum protein T4 binding sites. van Raaij et al. (1994) subsequently demonstrated a dose- and time-dependent uptake of pentachlorophenol into the cerebrospinal fluid of rats following single intraperitoneal injections. Since similar doses of pentachlorophenol also significantly decreased the uptake of radiolabeled T4 into cerebrospinal fluid, the study authors suggested that pentachlorophenol may interact with the T4 binding site of transthyretin and compete with T4 for uptake into cerebrospinal fluid (van Raaij et al. 1994). This is a plausible explanation since the affinity of pentachlorophenol for the T4 binding site on transthyretin is 2.5-fold greater than that of T4 itself (den Besten et al. 1991).

Such effects on thyroid parameters, combined with the activity of pentachlorophenol as a potent inhibitor of oxidative phosphorylation (Weinbach 1954), may be expected to have general adverse effects on basal metabolic rate and many critical processes including development, reproduction, nervous system function, and the specific functioning of endocrine and other organs.

In addition, the effects of pentachlorophenol on thyroid homeostasis and the availability of T4 to the central nervous system may have adverse effects on development of the nervous system. Deficiencies in T4 during prenatal and postnatal life can cause decrements in intellectual function in children (Bargagna et al. 1997; Birrell et al. 1983; Kooistra et al. 1994), and hypothyroidism in animals leads to disorders in structural and functional development of the brain (Gould et al. 1990; Neveu and Arenas 1996; Stein et al. 1991; Vega-Nunez et al. 1995). However, testing has not been performed on animals exposed to pentachlorophenol, either prenatally or postnatally, to examine the potential for the anti-thyroid effects of pentachlorophenol to produce adverse effects on neurobehavior. *In vitro*, pentachlorophenol binds microtubule-associated protein in hippocampal neurons, resulting in increased dendritic length; such disturbances in neurite outgrowth during development could result in altered neurological function (Matsunaga et al. 2010).

Recent studies in rats and mice involved the characterization of chlorinated protein adducts arising from pentachlorophenol metabolism following oral administration of pentachlorophenol (Lin et al. 1997; Waidyanatha et al. 1994, 1996). Results from these studies and previously summarized studies suggest that the metabolism of pentachlorophenol can proceed through the quinols, TCHQ and tetrachlorocatechol (Cl_4CAT), via microsomal cytochrome P-450 enzymes and that these quinols can be oxidized via semiquinone intermediates (tetrachloro-1,2-semiquinone [Cl_4-1,2-SQ] and tetrachloro-1,4-semiquinone [Cl_4-1,4-SQ]) into the corresponding quinones (tetrachloro-1,2-benzoquinone [Cl_4-1,2-BQ] and tetrachloro-1,4-benzoquinone [Cl_4-1,4-BQ]). Both the quinones and semiquinones are electrophilic and can bind to cellular macromolecules (Lin et al. 1997). The redox cycling associated with oxidation of TCHQ and reduction of Cl_4-1,4-BQ generates oxygen radicals that caused an increase in 8-hydroxy-2-deoxyguanosine levels in liver DNA in mice that had been fed pentachlorophenol (Sai-Kato et al. 1995; Umemura et al. 1996) or TCHQ (Dahlhaus et al. 1994) in the diet for up to 4 weeks. It is possible that the formation of such adducts is involved in the induction of hepatic neoplasms in mice (NTP 1989). Lin et al. (1997) measured levels of chlorinated protein adducts arising from pentachlorophenol metabolism in the livers of mice and rats administered pentachlorophenol in the diet for up to 4 weeks. After aggregation of the estimated contributions of all quinone species derived from pentachlorophenol metabolism, mice had a 4-fold greater dose to liver nuclei than rats, whereas rats had a

3-fold greater dose to liver cytosol than mice. The increased nuclear dose to mouse liver compared to that of the rat suggests that the mouse is at greater risk to hepatic DNA damage from pentachlorophenol-derived quinones. Using a model to predict quinone and semiquinone production, Lin et al. (1999) estimated that at low doses of pentachlorophenol, the production of semiquinone adducts was proportionally greater in rats than mice; in mice, direct oxidation to quinones and the production of quinone adducts is favored in mice exposed to low doses of pentachlorophenol. These data suggest that both the types and amounts of adducts differ in rats and mice, which may account for the occurrence of liver tumors in mice but not in rats in bioassays conducted by NTP (1989, 1999).